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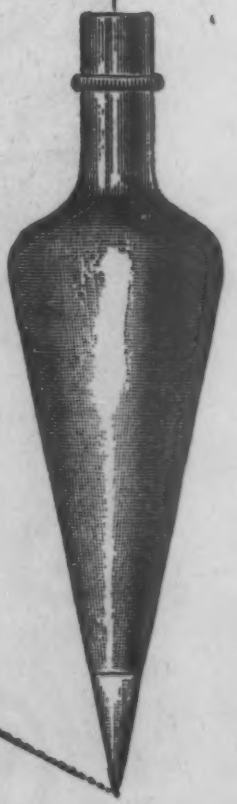

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ANNALS OF SURGERY

VOL. 126 AUGUST, 1947 No. 2

THE MANAGEMENT OF CARCINOMA IN THE SEVERAL PARTS OF THE COLON*

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NEW YORK, N. Y.

THOUGH NOT THE FIRST to practice delayed extraperitoneal resection in the surgical treatment of carcinoma of the colon, Mikulicz,[1] in 1903, was the first to report a series of cases treated in this manner. His publication of the results in 16 cases in which the carcinoma was first brought out of the abdominal cavity and later excised had a profound effect upon the surgical treatment of this disease. The principle of extraperitoneal resection became established almost immediately and still attracts many followers.

Acceptance of the exteriorization method, though widespread, was not universal. It has disadvantages in certain types of cases, particularly in obese patients with short mesentery, and interest in finding a safe method of performing primary resection and anastomosis was not lost.

The search took two general directions: First, there was the quest for an effective aseptic method of performing resection and anastomosis; and, second, efforts were directed toward getting the bowel into better condition before resection and suture were attempted. The endeavor to find a way to maintain asepsis led to the development of ingenious clamps and other devices intended to accomplish that purpose. Wangensteen,[2] who himself designed a clamp for anastomosis, states that Parlavecchio, an Italian surgeon, used a similar clamp as early as 1898 to 1900. The names of Parker and Kerr,[3] Schoemaker,[4] Fraser and Dott,[5] Scarff,[6] Rankin,[7] and many others, are associated with methods of aseptic, or closed, anastomosis.

The importance of having nondistended bowel of normal texture before resection and anastomosis are attempted was brought home to the earlier surgeons through grievous experience. It was gradually recognized that a high operative mortality prevailed when obstruction was present and a relatively low mortality, even with open anastomosis, when obstruction was

* Read before the New York Surgical Society, December 11, 1946.

absent. The advantages of having normal bowel to deal with became clear, and when medical means of evacuation were ineffectual it was natural that surgical drainage should be considered. According to Rankin,[8] the idea of external drainage of the distended bowel proximal to an obstruction was entertained as early as 1710 by Littré, who proposed colostomy for relief of obstruction due to malformation of the rectum, but it remained for Pillore, of Rouen, 66 years later, to actually perform a right inguinal colostomy for obstruction of the rectum due to tumor.

It is not clear who was the first to make a practice of draining the colon proximal to an obstructing growth in preparation for its removal. It may well be that the first colostomies producing this effect were more or less accidental. Hartwell,[9] for example, describes opening the abdomen for intestinal obstruction and finding a band over the distended cecum which had produced a slough. There was gross leakage, and to meet the situation he made a right intermuscular incision and sutured the margins of the hole in the cecum to the incised peritoneum and to the skin. Without previous design he, thus, established a cecostomy. The patient improved to such an extent that the obstructing tumor, a carcinoma of the splenic flexure, was later removed and the patient survived. Whatever the origin of the operations for proximal drainage of the colon, their usefulness in the presence of obstruction and other complications is now generally recognized. Mayo,[10] Bevan,[11] Crile,[12] Stiles,[13] Schoemaker,[14] Cheever,[15] Whipple,[16] Rankin,[17] Wilkie,[18] and Allen,[19] have had a noteworthy influence in developing an appreciation of these procedures.

The lowering of mortality has been accomplished not only by improved surgical management but also by a number of other factors. The introduction of the sulfonamide drugs, particularly the intestinal antiseptics succinylsulfathiazole (sulfasuxidine) and phthalylsulfathiazole (sulfathalidine) the efficacy of which has been demonstrated by Poth,[20] the more effective intestinal deflation by use of the Miller-Abbott tube, greater alertness in early diagnosis, and the increased competence of a greater number of surgeons, all have contributed to the safety of the operation. In addition to these advantages, there is a better understanding of the pathologic physiology associated with surgical operations, greater appreciation of the importance of fluid and protein balance, of vitamins, blood transfusion, and the numerous corrective measures which have contributed to the improvement of surgery in general.

As the safety of primary resection and anastomosis has increased, and fewer patients arrive with obstruction, there has been a growing tendency toward the performance of a one-stage instead of a two- or three-stage operation. Right colectomy for lesions without obstruction has long been performed as a one-stage procedure, but in the presence of obstruction or other complications resection has been preceded by ileocolostomy. Whipple,[21, 22] has reported strikingly favorable results from the use of the Miller-Abbott tube as a preoperative means of deflation, and finds that obstructive lesions of the right colon which previously would have required preliminary ileocolostomy may now be resected in one operation.

In planning the resection of an uncomplicated carcinoma, Campbell,[23] Stone and McLanahan,[24] Wangensteen,[2, 25] Waugh and Custer,[26] Meyer, Sheridan, and Kozoll,[27] and Zinninger and Hoxworth[28] no longer differentiate between the right and left portions of the colon, and may undertake a one-stage operation irrespective of the location of the tumor. They believe primary one-stage resection and anastomosis is safe in the left colon as well as in the right, provided there is minimal or no obstruction or other serious impediment.

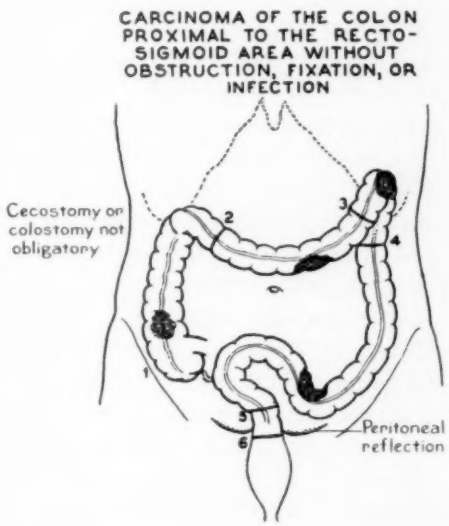

FIG. 1.—Colon divided into surgical segments.

1–2 Cecum, ascending colon, and hepatic flexure.
2–3 Transverse colon.
3–4 Splenic flexure.
4–5 Descending colon and sigmoid.
5–6 Rectosigmoid.

The diagrammatic representation of a tumor is shown in each segment except the rectosigmoid.

Considerable differences of opinion are found among the large clinics of this country concerning the merits of various operative procedures, particularly with respect to the Mikulicz-type of operation. Undoubtedly, these divergences of view have created uncertainty in the mind of the general surgeon who operates upon the occasional case. His experience with the disease has not been sufficient to permit him to have definite ideas based upon personal observations, and a review of the literature does not enable him to see clearly the course he should pursue.

On the one hand, he has the opinion of Lahey,[29, 30, 31] whose vast experience has confirmed him in the belief that the modified Mikulicz procedure is the safest operation for carcinoma of the large bowel, including the right colon. With respect to the right colon, however, there appears to be some deviation[32] from this rule. Almost diametrically opposed is Wangensteen[2] whose practice is to resect all unobstructed lesions of the colon in one stage, establishing intestinal continuity by oblique aseptic end-to-end anastomosis without antecedent or complementary colostomy or decompressive vents. Among those following a middle course are Rankin,[33] Allen,[19] White and Amendola,[34] and Coller and Vaughan[35] who may do either an obstructive resection or resection with immediate end-to-end anastomosis, but when the latter operation is elected ordinarily establish proximal drainage either as a preliminary measure or at the time of resection, except in unobstructed lesions of the right colon.

The results at the Lahey Clinic, where the modified Mikulicz procedure has been followed almost exclusively in the treatment of hundreds of cases, the results have been excellent. Whether they would have been better with resec-

tion and anastomosis we cannot know. As between the principles of exteriorization, and resection with aseptic end-to-end anastomosis, there can be little question but that the present trend is in favor of the latter procedure, with or without proximal drainage.

In hospitals where both types of operations are done in something like equal numbers the results generally favor closed resection and anastomosis. In a series of cases reported from St. Luke's and the New York Hospitals[36] the mortality was appreciably higher with the exteriorization procedures. In a subsequent study of cases from the Pennsylvania and Bryn Mawr Hospitals Gibbon and Hodge[37] found the mortality from exteriorization procedures more than twice that following closed resection with aseptic anastomosis, and in a compilation of statistics which included other clinics,[36, 38, 24] as well as their own, the mortality from exteriorization operations was 27 per cent, and for resection with aseptic anastomosis 14 per cent. In 1940, Patterson and Webb,[39] basing their study on cases treated at the Roosevelt Hospital, reported favorably on the Mikulicz procedure, but four years later, after having given aseptic resection and anastomosis a trial, White and Amendola,[34] in a review of cases from the same institution, found that the mortality from the Mikulicz operation was twice that resulting from resection with aseptic anastomosis. With these facts in mind, the present discussion of treatment will be concerned primarily with the latter method.

To attempt the formulation of rules to meet all the conditions which may complicate carcinoma of the colon or to prescribe operative procedures for all to follow would be presumptuous and futile. One cannot, however, review the experience of the many surgeons who have had a special interest in this disease and correlate it with his own without arriving at certain conclusions as to how carcinoma of the colon, as ordinarily encountered, should be treated.

If one elects closed resection with aseptic anastomosis, there are certain basic principles which must be observed. These were very well presented by Reichel,[40] in 1911:

1. The general condition of the patient must be such that a somewhat lengthy operation is permitted.

2. The intestine proximal to the tumor must not harbor any considerable accumulation of fecal material.

3. The intestine must be viable and free of circulatory disturbance.

4. It must be possible to suture the ends of intestine together without tension.

Reichel, furthermore, admonished care in placing the sutures so that the approximation should be accurate. He believed that poor results were due to emphasis upon speed of operation rather than upon exactitude. Little fault is to be found with Reichel's criteria, and if any one condition is to be stressed above the others it is that the intestine must be viable and free of circulatory disturbance. Such favorable conditions cannot exist in the presence of obstruction.

It may be stated as a corollary to Reichel's rules, that if the bowel is not

in a suitable state for primary resection and anastomosis, the operation should not be attempted until the adverse conditions have been corrected. Any restriction upon immediate resection, such as obstruction, local infection, or fixation, must be corrected before the definitive operation is attempted. In the occasional case it is impossible to attain wholly favorable conditions for operation and known risks must be accepted. However, the surgeon in his desire to hasten the patient's recovery must not be tempted to take risks which might be avoided by a less hasty plan.

For the purpose of discussing operative procedures, the colon often is divided simply into right and left halves. The problems of surgical management of carcinoma in certain parts of the two main segments, however, require more specific treatment and for convenience in discussion a more detailed segmentation is offered (Fig. 1). Consideration will be confined largely to surgical management and surgical principles rather than to technical details, such as methods and materials employed. These have been considered in a previous publication,[36] and are described in a number of recent contributions.[23, 2, 28, 41]

CARCINOMA WITHOUT OBSTRUCTION, FIXATION, OR INFECTION

It is becoming increasingly evident that in the absence of obstruction, fixation, or infection, a carcinoma in almost any part of the colon may be resected and continuity immediately restored without undue risk. Appreciable obstruction, fixation, or infection are contraindications. In dealing with the right colon, Whipple's[22] more recent experience has led him to believe that with suitable preparation of the bowel and care in performance the open suture technic is as safe as the so-called aseptic methods. Meyer, Sheridan, and Kozoll[27] have arrived at similar conclusions with respect to the left colon. This does not agree with the findings of Stone and McLanahan.[24] It would appear logical that the closed technic involves less contamination and is the better procedure.

In conceding the general applicability of primary resection and anastomosis to the uncomplicated carcinoma of the colon, reservations should be made with respect to the splenic flexure and the rectosigmoid segment. These will be discussed under the appropriate headings.

CARCINOMA WITH OBSTRUCTION, FIXATION, OR INFECTION

The presence of appreciable obstruction, fixation, or infection in association with a colonic carcinoma precludes the safety of immediate resection and anastomosis. The harmful effects of obstruction on the blood supply, viability, and tenacity of the proximal bowel wall are well-known and are more important than the bowel content.

The dangers of fixation reside in the fact that it renders mobilization difficult, and adjacent structures may be damaged by attempts to free the tumor. Furthermore, fixation may be associated with infection, often with abscess

formation, and efforts to detach the tumor from its surroundings may lead to gross contamination through accidental opening of the bowel, or by breaking into an abscess. The importance of draining the proximal obstructed colon for a period of several days before resection is attempted, and the risks of failure to drain cannot be questioned.

With the general principles of resection in mind we may proceed to a more detailed discussion of treatment according to the part of colon involved.

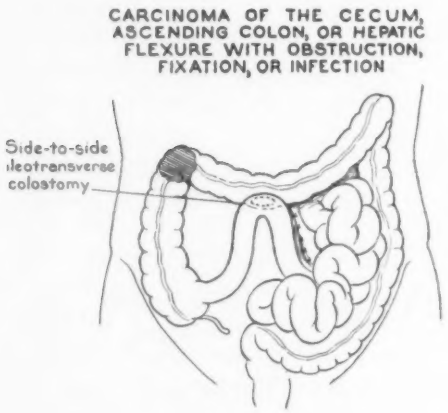
CARCINOMA OF THE CECUM, ASCENDING COLON, OR HEPATIC FLEXURE WITH OBSTRUCTION, FIXATION, OR INFECTION
Side-to-side ileotransverse colostomy

FIG. 2.—Obstructing carcinoma of the right colon (hepatic flexure) with side-to-side ileotransverse colostomy performed. Note closure of space between mesenteries of terminal ileum and transverse colon.

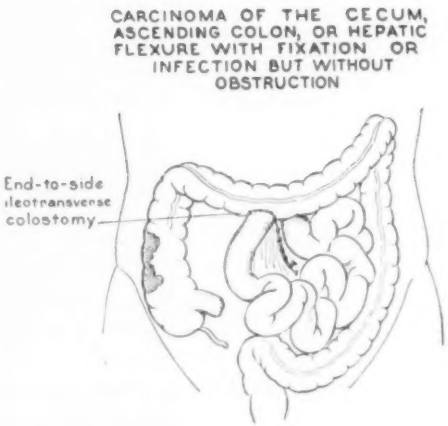
CARCINOMA OF THE CECUM, ASCENDING COLON, OR HEPATIC FLEXURE WITH FIXATION OR INFECTION BUT WITHOUT OBSTRUCTION
End-to-side ileotransverse colostomy

FIG. 3.—Carcinoma of right colon with fixation or infection, but without obstruction. End-to-side ileotransverse colostomy has been done, and closed end of distal segment of ileum returned to usual position.

1. CECUM, ASCENDING COLON, AND HEPATIC FLEXURE

This portion of the colon, constituting almost its entire right half, may be discussed as a unit; operative treatment for carcinoma in any part of it is essentially the same. The treatment consists of resection of the entire segment with restoration of continuity by ileotransverse colostomy. In the absence of obstruction, fixation, or gross infection, the operation is ordinarily done in one stage. If obstruction is present a preliminary side-to-side ileotransverse colostomy is done (Fig. 2), with resection following in approximately two weeks. If fixation or infection is present without obstruction, an end-to-side ileotransverse colostomy may be done and the closed distal end of the ileum returned to the abdominal cavity (Fig. 3). After the preliminary ileotransverse colostomy, inflammation subsides; at the second operation the mass often is found surprisingly mobile and may be resected with ease.

With either procedure, it is important to close the opening between the mesentery of the proximal segment of ileum and that of the transverse colon. Allen[19] mentions a fatal case of obstruction of the small bowel from herniation

through the trap left by the preliminary ileotransverse colostomy. After ileocolostomy has been completed, there should be no resort to external drainage of any kind. It accomplishes nothing and carries with it all the dangers and disagreeable features associated with external small intestinal fistulae.

In doing a closed ileocolostomy, one must be sure that the triangular piece, or pieces, of bowel wall grasped by the clamps include mucosa. This can be determined by inspecting the portions of wall removed. To be sure of patency after anastomosis, the finger is used to invaginate bowel wall through the stoma.

One may ask why it is necessary to do a complete extirpation of the right colon, even for a small tumor of the cecum or ascending colon. The answer lies mostly in the fact that the ileocolic group of lymph nodes, as Jamieson and Dodson[42] found, extends as high as the duodenum. The distribution of the blood supply is also a consideration. Steward and Rankin,[43] and Singleton[44] have called attention to rather frequent anomalies of the blood vessels of this and other parts of the colon. Resection of the right colon is sometimes regarded relatively safe as compared with the more distal segments. Allen,[19] however, reminds us that in most clinics operative mortality remains greater in this segment than elsewhere.

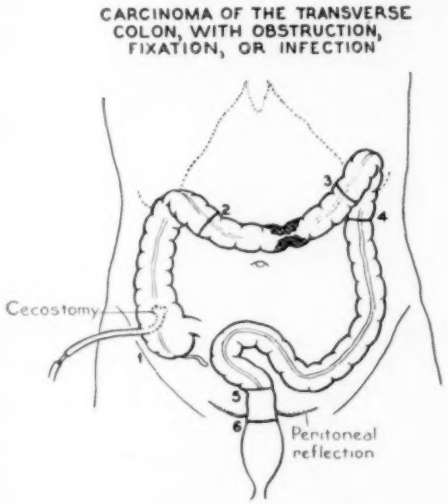

FIG. 4.—Carcinoma of transverse colon with obstruction, fixation or infection. Drainage of proximal colon by cecostomy.

2. TRANSVERSE COLON

In this segment, due to its large caliber and fluid content, obstruction is the exception. Furthermore, the transverse colon is relatively superficial and tumors situated in it may be felt before they reach large size. Tumors of the transverse colon ordinarily are well-suited to primary resection and anastomosis without proximal drainage. Mayo and Simpson,[45] reporting a series of cases, found that the mortality for exteriorization procedures was 20 per cent, whereas the mortality following resection with primary anastomosis was 11.1 per cent. The middle colic artery comes in for special consideration because of the dependence of almost the entire transverse colon upon it and the frequent necessity of resecting a portion of it with the tumor. The viability of the ends of colon to be sutured together must be assured before the anastomosis is made. In some cases it is necessary to mobilize the splenic or hepatic flexure in order to bring viable ends together.

In the occasional case with obstructions, proximal deflation can be satis-

factorily accomplished by cecostomy (Fig. 4). If distention is extreme, and the cecal wall is greatly thinned, it is better, as Rankin[17] suggests, to seal off the anterior cecal wall and deliberately puncture it with a small needle. After the gas has escaped the cecostomy can be performed with less danger of accidental rupture. The bowel should be irrigated daily to insure evacuation of the

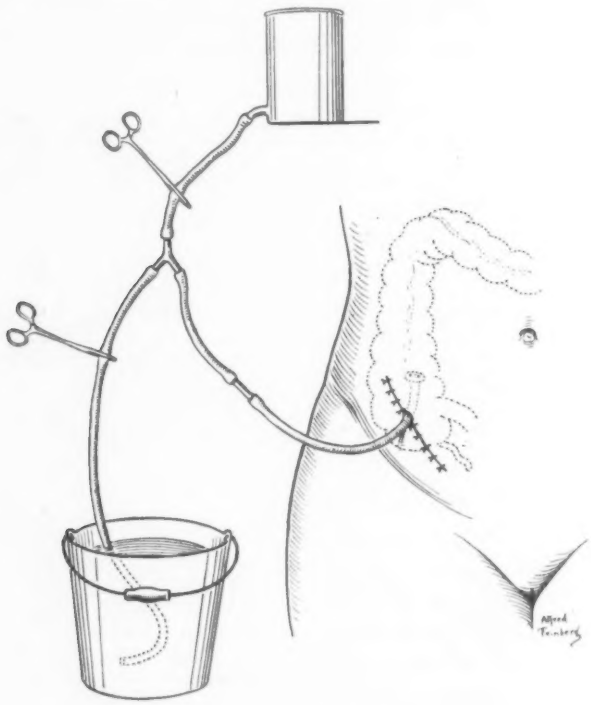

FIG. 5.—Simple apparatus for irrigating colon through cecostomy prior to resection. The flow of water from irrigating can is controlled by means of the two hemostats. The cecostomy tube is a mushroom (Pezzar) catheter, the tip of which has been cut off. The fecal return is received by the pail below.

accumulated feces and to keep it deflated. A convenient apparatus for this purpose is shown in Figure 5. As a rule, ten to 14 days after cecostomy, resection can be carried out with safety. Irrigations should be suspended until the anastomosis is secure and then resumed with care. As soon as bowel movements by rectum have started, the cecostomy tube may be withdrawn and the wound given opportunity to heal. If spontaneous healing fails or is long delayed, the opening may be closed surgically.

3. SPLENIC FLEXURE

The splenic flexure comprises the splenic angle with approximately 10 cm. of colon on either side. Carcinoma arising in this segment requires special consideration for several reasons:

1. The symptoms, due mainly to beginning obstruction, are obscure, and are often referred to parts of the abdomen remote from the site of the tumor. The treatment for a long period of time may be based on an erroneous diagnosis.

2. Tumors of the splenic flexure ordinarily are high under the costal margin near the posterior abdominal wall and cannot be palpated until they reach large dimensions.

3. The proximal segment of the splenic flexure lies anterior to the distal segment and a carcinoma situated in either may not be revealed by the usual

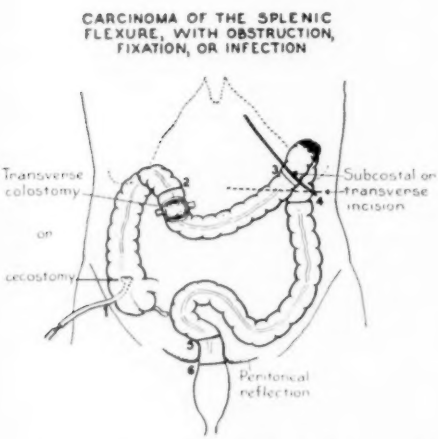

FIG. 6.—Carcinoma of splenic flexure with obstruction. Proximal deflation and drainage are effected by cecostomy or transverse colostomy. Fixation or infection require the same treatment. Possible approach through anterior subcostal or transverse incision is indicated.

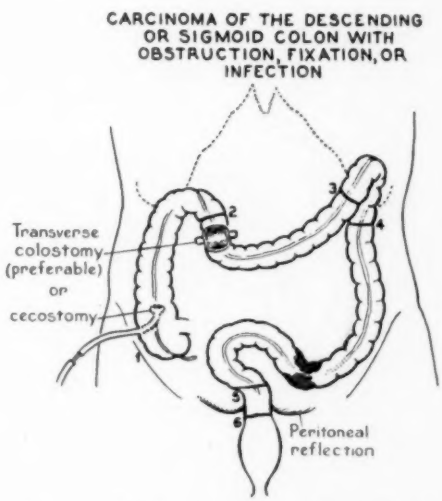

FIG. 7.—Carcinoma of descending or sigmoid colon with obstruction, fixation, or infection. Proximal drainage by cecostomy or transverse colostomy, preferably the latter, is required. Resection should be delayed 10 to 14 days.

anteroposterior roentgenogram. If examinations are not made in the oblique view the tumor is likely to be missed.

4. Tumors in the splenic flexure are frequently of the annular type and complete obstruction is often the symptom that leads to recognition.

5. Because of the delay in diagnosis, perforation with abscess formation is common in this region.

6. Fixation of the tumor is a frequent complication.

7. Surgical access is difficult, particularly in obese patients.

All of these possibilities forecast the frequency of complications in carcinoma of the splenic flexure and warrant the setting apart of tumors in this region for particular attention. Preliminary cecostomy, or transverse colostomy will prove an aid often enough to justify routine use. Proximal drainage is seldom a disadvantage, and may be extremely helpful.

The surgical approach to the splenic flexure usually is more difficult than that to other segments and an anterior subcostal, or transverse incision is advantageous (Fig. 6). An incision below and parallel to the posterior rib margin, described by Hoag,[46] appears to have merit. Exaggerated fear in regard to healing of the transverse incision and its modifications need not be entertained.

4. DESCENDING COLON AND SIGMOID

Enough experience has accumulated to prove that uncomplicated tumors in this segment may be resected without serious risk after a thorough preparation of the bowel by conservative means. Annular growths producing partial or complete obstruction, however, are common in the long segment of colon. When there is a history of intermittent or persistent obstructive symptoms or evidence of fixation or infection, it is safer to do a cecostomy or transverse colostomy (Fig. 7) and delay resection until the bowel has had a sufficient period of deflation to regain its normal properties. Ordinarily this is a matter of 10 to 14 days, depending upon the degree of obstruction or the severity of other complicating factors.

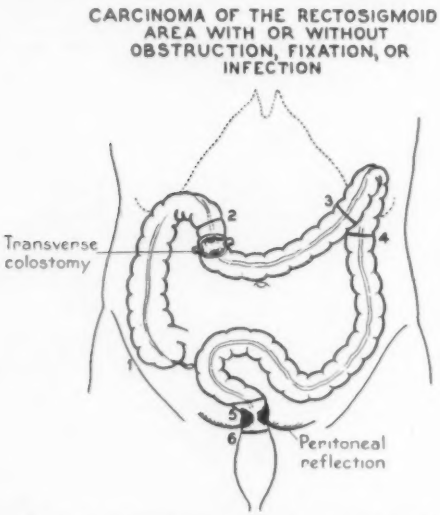

FIG. 8.—Carcinoma at the rectosigmoid with or without obstruction. Complete diversion of feces by transverse colostomy 10 to 14 days prior to resection is required. If the tumor is fixed, or gross infection is present, the success of anastomosis to the lower segment is doubtful.

The differentiation between diverticulitis and carcinoma is sometimes a problem. The two conditions simulate each other very closely. There are few symptoms of one which cannot be attributed to the other. The demonstration of diverticula in the roentgenograms does not rule out cancer. The diagnosis can be established in most instances by repeated fluoroscopic observations with the aid of the barium enema. If drainage of the proximal bowel is carried out in the belief that an obstruction is caused by carcinoma when in fact it is due to diverticulitis, roentgenograms taken several days later may show that the obstruction has largely disappeared. When diverticula are known to be present, it is well to repeat the roentgenologic examination before resection of a lesion presumed to be carcinoma is undertaken.

The descending colon often requires considerable mobilization before satisfactory anastomosis can be established but it must be freed even more if an exteriorization procedure is done. The sigmoid, because of its length and mobility, is perhaps the most adaptable part of the colon for the Mikulicz-type of operation; but for the same reasons it also lends itself well to resection and immediate anastomosis.

5. RECTOSIGMOID

This segment of colon (Fig. 8) has been variously defined, but for practical purposes a tumor may be said to be in the rectosigmoid when its excision requires transection of the bowel below the level of the reflection of the pelvic peritoneum. After the resection of such a tumor, the success of an end-to-end suture is imperiled by certain characteristics of the lower segment which limit its adaptability for secure union with the upper segment:

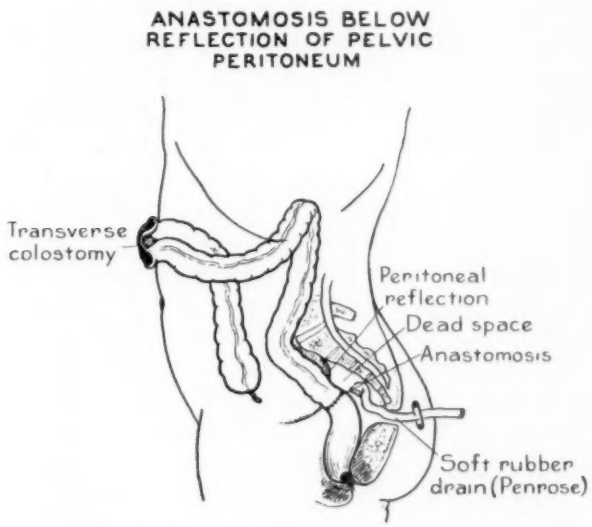

FIG. 9.—Drainage of space about anastomosis situated below pelvic peritoneal floor is accomplished by resecting the coccyx and inserting a soft rubber drain of the Penrose-type through its bed.

1. The lower segment lacks the visceral peritoneal investment which contributes so much to dependable apposition and prompt healing.

2. The perirectal tissues lying below the pelvic peritoneal floor are highly susceptible to infection.

3. Surgical access to this region is difficult.

In spite of these disadvantages there has been no lack of effort on the part of surgeons to restore continuity of the bowel and preserve the function of the sphincters. Kraske's[47] operation, described in 1885, was designed primarily for high carcinomas of the rectum, and when possible restored continuity by suture through a sacrococcygeal approach. Hochenegg[48] brought the upper segment of resected bowel down through the rectal sphincters and sutured it to the anal margin. Balfour[49] introduced through the rectum a large tube to which the upper segment was attached and partially telescoped into the lower. Crile[12] did a low end-to-end anastomosis through an abdominal approach in much the same manner the operation is now performed by Dixon,[50, 51] and Wangensteen.[2, 25] Crile preceded the operation by a complete diversion of the

fecal stream through a transverse colostomy. In addition to a transabdominal operation for the resection of carcinomas eight centimeters, or more, from the anal outlet, Mahorner[52] has described a technic for combined abdomino-ischial resection, applicable to low rectal growths, with preservation of the sphincters.

Resection of carcinoma of the rectosigmoid with end-to-end suture through an abdominal approach is a practicable operation in the average case. As the level of the tumor descends, however, the risks of the operation rise rapidly. Rather frequent infection and leakage at the site of anastomosis have been recorded by Wangensteen,[25] and by Waugh and Custer.[26] Wangensteen, who performs the operation without preliminary drainage or diversion of feces in the proximal colon, reported primary healing in only a minority of anastomoses following resection of tumors less than 10 cm. from the anus. Waugh and Custer mentioned cases in which there was drainage of an abscess into the rectum.

The risks of leakage and infection are materially reduced if the line of anastomosis falls within the peritoneal cavity, or if the pelvic floor can be reëstablished below the anastomosis, as recommended by Allen.[19] Intraperitoneal resistance to infection is greater than that of the extraperitoneal tissues and healing is promoted by the adherence of peritoneum at the suture line. If the anastomosis necessarily lies below the peritoneal floor, drainage of the surrounding space is a required measure. This can be done suprapubically, as practiced by Dixon[50, 51] or through an opening established immediately anterior to the tip of the coccyx, as advocated by Wangensteen.[25] More effective drainage, however, is secured by removing the coccyx and establishing a vent through its bed (Fig. 9). The drain should be of thin, soft rubber, such as the Penrose-type. A thick or hard tube may impinge on the bowel and produce necrosis. The judicious use of the antibiotic drugs affords considerable security against fulminating infection in this region. One of the greatest single measures of safety in resection and suture at the rectosigmoid level is a transverse colostomy performed several days in advance and completely diverting the feces.

In their conclusions, Stone and McLanahan[24] regard immediate resection, immediate anastomosis, and utilization of aseptic technic as the ideal type of operation for carcinoma of the colon. There can be no disagreement with this definition of the ideal, which finds practical application in the uncomplicated case. The drawback resides in the fact that it is often impossible to know in advance just what complications, if any, exist, and what measures may be necessary to cope with them. There may be, for example, an unsuspected inflammatory process about the tumor, multiple adhesions of other viscera to it, or a walled-off perforation. If the bowel proximal to the lesion has first had a period of partial or complete rest through cecostomy or colostomy, it should be in the best possible condition for whatever operative procedure is necessary.

When primary resection is intended and an unforeseen complication is encountered, there is always the inclination to proceed with the definitive

operation as planned, bearing in mind, but at the same time disregarding, the fact that conditions for the operation are not ideal. The result may be chastening to the surgeon, and irreparably bad for the patient. If exploration reveals that immediate resection and anastomosis are definitely not practicable, the decision to do a cecostomy or transverse colostomy, and wait, is not difficult. It is the middle ground case that offers the greatest temptation and, therefore, the greatest danger.

CONCLUSIONS

1. Uncomplicated carcinoma of the cecum, ascending colon, and hepatic flexure may be resected and ileotransverse colostomy performed at a single operation. In the presence of obstruction, fixation, or infection, ileotransverse colostomy should be done first with resection following later.

2. Carcinoma of the transverse colon ordinarily may be resected and anastomosis established as a one-stage operation. Obstruction, extensive fixation, or infection calls for a preliminary cecostomy.

3. Carcinoma of the splenic flexure is often recognized late, complications are frequent, and surgical approach may be difficult. Preliminary cecostomy or transverse colostomy should be the rule, with primary one-stage resection reserved for the exceptional case. Transverse, or subcostal incision provides a good exposure.

4. In the descending and sigmoid colon, primary resection and immediate anastomosis are permissible provided there are no complications. Obstruction, fixation or gross infection requires proximal drainage by cecostomy or transverse colostomy, preferably the latter. Diverticulosis may confuse the diagnosis and treatment.

5. At the rectosigmoid level, preliminary transverse colostomy with complete diversion of feces is a prerequisite to resection with immediate anastomosis. Faulty healing of the suture line frequently results in leakage, infection, and fistulae. The presence of feces in such a field is a serious disadvantage.

6. The space about an anastomosis established below the level of the pelvic peritoneal floor should be freely drained through the coccygeal bed.

7. Primary one-stage resection and anastomosis may succeed in any part of the colon proper, but it should not be performed for tumors in the rectosigmoid and its use elsewhere should be limited to uncomplicated lesions.

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CARCINOMA OF THE THYROID

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ALTHOUGH most thyroid cancer occurs in nodular goiters, the incidence of malignant tumors in nodular goiters has been regarded by many physicians as too low to be accepted as a valid indication for their routine removal. However, as the operative risk has declined, it has become probable that life can be saved by taking a more radical attitude toward nodular goiters. This view was recently emphasized by Hinton and Lord[10] who found the incidence of carcinoma to be 7.6 per cent in clinically benign nodular goiters as compared to an incidence of 6.7 per cent carcinoma in clinically benign breast lesions. The good prognosis in the group of thyroid cancers found histologically in nodules not suspected of malignancy upon physical examination is another point in favor of the early removal of all nodular goiters.

The importance of both surgical and radiotherapeutic methods in the treatment of thyroid cancer is generally recognized. Surgical removal, in the case of operable tumors, is usually the initial treatment and there are many cases of carcinoma of the thyroid in which the indications for treatment by some form of radiation are clear-cut and beyond dispute. On the other hand, the value of routine postoperative irradiation for thyroid cancer is not a matter of general agreement. Lahey, Hare and Warren[13] recommend postoperative radiotherapy for all carcinomas of the thyroid, regardless of the pathologic type or extent of the tumor, whereas Portmann[17] considers that such routine treatment is of no benefit in those cases in which the diagnosis of carcinoma was made only after microscopic examination of the excised thyroid tissue, and of questionable benefit in those cases in which the tumor, although suspected clinically, remained confined within its capsule.

It is in an attempt to evaluate our experience with thyroid cancer, and especially to determine as far as possible the indications for postoperative radiotherapy, that we have reviewed the cases of carcinoma of the thyroid treated in the Hospital of the University of Pennsylvania since July, 1933.

INCIDENCE

During the period from July 1, 1933 to December 31, 1944, 2,079 lesions of the thyroid have been observed in the Laboratory of Surgical Pathology of the Hospital of the University of Pennsylvania. These have been classified in Table I.

If the 944 toxic and nontoxic diffuse goiters included in this series are eliminated from the computations, the incidence (among nodular thyroid enlargements) of adenoma becomes 10.1 per cent, of papillary cystadenoma

TABLE I

	Number	Per Cent
Diffuse toxic goiter	923	44.4
Diffuse nontoxic goiter	21	1.0
Nodular nontoxic goiter	637	30.6
Nodular toxic goiter	279	13.4
Chronic thyroiditis	30	1.4
Tuberculosis	1	0.1
Adenoma	115	5.5
Papillary cystadenoma	11	0.5
Carcinoma	62	3.0
Total	2,079	99.9

1.0 per cent and of carcinoma 5.5 per cent. These figures for the incidence of carcinoma—3.0 per cent of all surgically treated goiters (2,079) and 5.5 per cent of surgically treated *nodular* goiters (1,135)—are comparable to those of Ward,[21] whose figures, based on a considerably larger series than ours, are 3 per cent and 4.8 per cent, respectively. Cole, Slaughter and Rossiter[3] report that 7.2 per cent of the 523 nodular goiters they observed were malignant, and Stout[20] reports that 2.5 per cent of the 4,671 goiters of all types treated surgically at the Presbyterian Hospital in New York between 1924 and 1944 were malignant. Brenizer and McKnight[1] noted an incidence of carcinoma of 4 per cent in 2,324 patients with nodular goiters.

In the series of cases of thyroid carcinoma which we have analyzed we have included, in addition to the 62 cases noted above, five patients who had no surgical treatment but on whom autopsy material is available, three patients, also dead, on whom no pathologic material is available but whose clinical courses leave little doubt as to the diagnosis (all had roentgenographic evidences of metastases) and one case in which a pathologic diagnosis was made elsewhere and confirmed in this laboratory but in which the material is no longer available and cannot be reviewed for pathologic classification (Table II).

TABLE II

CASES OF THYROID CARCINOMA OBSERVED AT THE HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA

July 1, 1933 – December 31, 1944

Cases treated surgically (HUP)	62	
Autopsied cases (no surgical treatment)	5	
Total cases in which pathologic material is available		67
Cases treated surgically elsewhere (pathologic diagnosis made but material not now available)	1	
Cases diagnosed clinically (with roentgenographic evidence of metastases)	3	
Total cases		71

We have excluded several patients diagnosed clinically as having carcinoma of the thyroid but who died or were lost from follow-up with evidences of local disease only and who, therefore, may have had chronic thyroiditis rather than

neoplasm. Such exclusions are more or less balanced by the exclusion of several living patients who possibly, or probably, had malignant thyroid lesions but with regard to whom the clinical data are insufficient or the pathologic material inadequate to assure us of the diagnosis. During this 11.5-year period, then, 71 cases of carcinoma of the thyroid have been observed and treated in the Hospital of the University of Pennsylvania.

AGE

Seventy per cent of this series of thyroid carcinomas were recognized in patients between the ages of 41 and 70, an age-incidence very similar to that reported by Ward.[21] Our series includes one patient 19 years old, and 17 between the ages of 25 and 40 years. Although it is not apparent in our material, the occurrence of thyroid cancer in childhood is well known.[8, 15]

Portmann[17] has classified thyroid carcinomas according to the extent of the disease as follows:

GROUP I.—Cases without clinical evidence of malignant tumors of the thyroid gland, the neoplasms being small and discovered only after microscopic examination of tissues removed.

GROUP II.—Cases without clinical evidences of malignant tumors of the thyroid gland or their presence suspected only on the basis of the age of patients and recent rapid enlargements of goiters of long-standing, or discovered at operation or microscopic examination and the tumors still localized within the capsule of the glands.

GROUP III.—Cases with clinical or pathologic evidences of malignant tumors of the thyroid gland which had invaded or extended outside of the capsules of the thyroid glands but without clinical or roentgenologic evidences of metastases.

GROUP IV.—Cases with clinical or pathologic evidences of malignant tumors of the thyroid gland and also clinical or roentgenologic evidences of metastases.

TABLE III

AGE DISTRIBUTION OF PATIENTS WITH THYROID CARCINOMAS (CLASSIFIED ACCORDING TO PORTMANN'S METHOD)

Portmann's Group	Total No. Pts.	No. Pts. under 50 Yrs. of Age	Per Cent
I	27	19	70
II	5	4	80
III	23	7	30
IV	15	6	40
Total	70*	37	53

* The clinical data are insufficient to classify one patient according to this method.

Classification of the present series by this method (Table III) brings out the interesting observation that 70 per cent of the patients in Groups I and II were less than 50 years old, whereas, of the patients in Groups III and IV, only 34 per cent were under 50 years of age, when they first came under our observation.

SEX

Fifty-four, or 76 per cent, of the patients in our series were women, a ratio of approximately three females to one male. Ward[21] reports a sex ratio of one man to three or four women for malignant goiter and he, as well as Cole, and his associates,[3] and others, note even greater preponderance of other thyroid lesions in the female sex.

THYROTOXICOSIS

Of this group of 71 patients with thyroid carcinoma, two (3 per cent) showed unequivocal evidences of hyperthyroidism and in four others there was less definite, or questionable, evidence of thyrotoxicosis. Although carcinoma is rare in toxic diffuse goiter (Ward[21] encountered only one carcinoma in 1,900 toxic diffuse goiters, and Cole and his associates[3] one in 435 cases), the association of clinical manifestations of thyrotoxicosis with malignant lesions of the thyroid is not uncommon and has been reported to occur in as high as 33.5 per cent of a series of 245 cases of thyroid carcinoma by Pemberton and Lovelace.[15] Goetsch[5] has described nine carcinomas in diffusely hyperplastic goiters. One of our unquestionably toxic patients died as a result of the carcinoma, the other, whose carcinoma was small, and an incidental pathologic finding, is alive and well more than nine years after surgical excision.

RELATIONSHIP OF CARCINOMA TO NODULAR GOITER AND ADENOMA

Cole, and his co-authors[3] have emphasized the frequency with which nodular goiters may become malignant. Eleven per cent of the 100 nontoxic multinodular goiters in their series were identified as carcinomas, and no less than 24 per cent of the solitary nontoxic nodules were malignant. Lahey, Hare and Warren believe that 80–90 per cent of thyroid tumors arise from preëxisting adenomas, a conclusion with which most writers are essentially in agreement. Lahey,[14] and Warren[22] also emphasize the frequency with which the solitary nodule proves to be malignant. There is ample evidence that a large proportion of the carcinomas in our series had their origin in preëxisting benign tumors, but in many cases our material and data are not sufficiently complete to permit us to reach any definite opinion on this point. However, 74 per cent of the patients in this series gave a history of a preëxisting goiter of at least one year's duration and 42 per cent had a history of a goiter of at least five years' duration. Many of the goiters had been present for 10 to 15 years, or longer, and three for more than 35 years. The history of preëxisting goiter was most striking in the cases of Group I (Portmann's classification), all of which had a history of a goiter of at least one year's duration and 69 per cent of which had had a goiter for five years, or more.

PATHOLOGIC CLASSIFICATION

The pathologic classification we have used is essentially that proposed by Warren.[23] However, we have frequently found it difficult or impossible to distinguish between malignant papillary cystadenoma and papillary adenocarci-

noma and, therefore, placed all the papillary tumors in a single group and listed them, along with the malignant adenomas, as tumors of low or potential malignancy. With regard to this point, it is of interest that Lahey, Hare and Warren[13] report a higher incidence of five-year survivals (80 per cent) for papillary adenocarcinomas, which they consider to be of an intermediate grade of malignancy, than for the potentially malignant papillary cystadenomas with blood vessel invasion (62 per cent). Ward[21] classifies the malignant adenoma as of a higher grade of malignancy than the papillary carcinoma. The classification of the 67 cases in our series on which pathologic material is available is given in Table IV. We have followed Stout[20] in grouping the Hürthle cell carcinoma with the less malignant tumors, especially since the single case of this type in our series was a clinically unsuspected, encapsulated tumor which did, however, show intravascular growth.

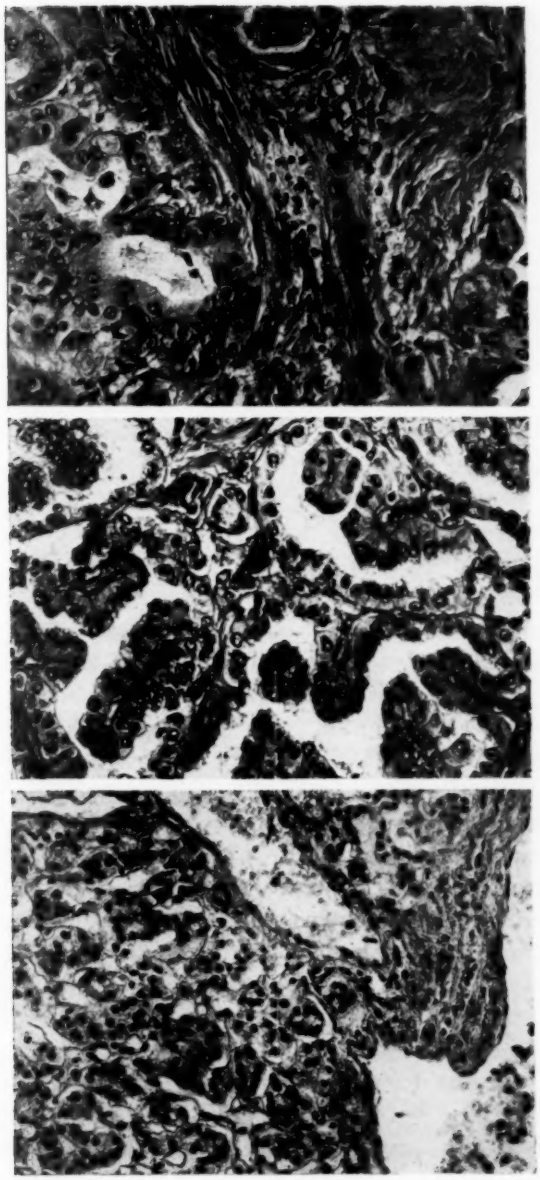
TABLE IV

	Number	Per Cent
I. Low degree of malignancy:	41	61.5
Malignant adenoma	20	30
Papillary carcinoma	20	30
Hürthle cell carcinoma	1	1.5
II. Moderate degree of malignancy:		
Adenocarcinoma	18	27
III. High degree of malignancy:	8	11.5
Small cell carcinoma	1	1.5
Giant cell (and spindle cell) carcinoma	7	10

In the case of tumors showing a variable histologic picture, we have classified them according to the predominant type of growth (Fig. 1). The relative numbers of each type show a distribution not very different from that reported by Cole, and his associates,[3] and by Stout.[20] We did not encounter any squamous cell tumors in this study. Although small areas of squamous cell differentiation were present in several of our carcinomas, this type of tissue did not predominate in any case. Two of the tumors in this series were composed almost entirely of spindle-shaped cells. Both showed areas indicating their carcinomatous nature, and in one case there were colloid-containing follicles in a uterine metastasis.[19]

METASTASIS

Metastases occurred in 25 of these 71 patients. There were 33 different sites of involvement, the most frequent being the cervical lymph nodes (11 times), bones (nine times) and lungs (six times). The liver, cerebrum and mediastinal nodes were each involved twice and the uterus once. Multiple metastases were especially noteworthy in the cases with bone lesions, one patient showing widespread involvement of the entire osseous system. The femur was involved in four instances, the bones of the skull and pelvis each in three instances and the sacrum twice. Single cases showed metastases in the thoracic and lumbar spine, rib, humerus, radius and mandible.



A B C

FIG. 1.—(A) Carcinoma of thyroid of malignant adenoma type (with blood vessel invasion).
(B) Papillary carcinoma of thyroid.
(C) Adenocarcinoma of thyroid.

BLOOD VESSEL INVASION

Definite histologic evidence of blood vessel invasion was encountered in 36 (54 per cent) of 67 cases. We have not found intravascular growth to be of significance in the prognosis of thyroid cancer. Twenty-four of the cases in which this finding was present have been followed for three years, or more, and 11 of them are without symptoms, and have survived for periods of from three to 12 years. On the other hand, as originally pointed out by Graham,[6] blood vessel invasion is an extremely useful and important diagnostic criterion. Its importance is greatest in the adenoma malignum group, where the diagnosis of malignancy must not infrequently rest largely, or wholly, upon the basis of this finding.[13]

RESULTS OF TREATMENT

There is general agreement in the literature upon surgical removal as the initial treatment of choice in thyroid cancer. Indeed, as already pointed out, the diagnosis is frequently unsuspected until after surgery has been performed. There is similar general agreement upon the efficacy of radiation therapy, especially for papillary tumors.[7, 9, 16, 17, 18, 23] Lahey, Hare and Warren[13] recommend postoperative radiation in all cases in which a diagnosis of carcinoma is made, regardless of the type or extent of the tumor.

Our series includes several cases in which surgical removal of a carcinoma of the thyroid was known to be incomplete, but in which the disease has been arrested by radiation therapy, and the patients have survived without symptoms over long periods of time. One such patient is alive and well 7.5 years after incomplete removal of an adenocarcinoma; another is alive and without symptoms eight years after simple biopsy of a papillary carcinoma. A number of other patients have survived for 2 to 4 years following incomplete extirpation or biopsy and irradiation. Some of the patients in this last group have subsequently died, but several are alive and are asymptomatic.

It must be remembered, however, that, in cancer of the thyroid in particular, we must be cautious in speaking of "cures," since many patients remain well for five, or more, years following the diagnosis of carcinoma and the initial treatment only to succumb later with extension of the malignant disease. Our series includes one patient who developed a metastasis in the humerus after eight asymptomatic years following thyroidectomy for an adenocarcinoma. Her arm was amputated, and she remained well for another three years before developing multiple bone metastases. This patient was a "ten-year survival" although she eventually died as a result of her thyroid carcinoma.

Nevertheless, in the light of our experience, there can be no doubt of the value of roentgenotherapy, even though we may never be assured of permanent cures by this means. Among the patients we have studied there is one who had a small cell carcinoma (Fig. 2), and who is alive and well ten years after surgical removal and irradiation, and one patient with a giant cell carcinoma (Fig. 3) who survives ten years after partial surgical removal and postoperative roentgenotherapy. Both of these patients had tumors of a pathologic type

which Ward[21] considers hopeless. We have briefly noted instances of favorable results in cases of four different pathologic types, but it should be added that our experience is in agreement with that of others in that the papillary carcinomas appear to be more radiosensitive than other types.

In Table V our five- and ten-year survivals are listed according to the pathologic classification of the tumors. Table VI lists the survivals according to Portmann's[17] classification. In each table the survivals — those patients known to be living and without symptoms—have been computed on the basis of the total number of patients treated more than five (or ten, as the case may be) years ago.

TABLE V

FIVE- AND TEN-YEAR SURVIVALS ACCORDING TO PATHOLOGIC CLASSIFICATION

Type of Tumor	No. of Pts. Treated more than 5 Yrs. ago	5-Yr. Survivals No.	5-Yr. Survivals Per Cent	No. of Pts. Treated more than 10 Yrs. ago	10-Yr. Survivals No.	10-Yr. Survivals Per Cent
Malignant adenoma	13	7	54	4	2	50
Papillary carcinoma	11	7	64	6	4	67
Malignant adenoma and papillary ca. (together)	24	14	58	10	6	60
Adenocarcinoma	12	6	50	6	3	50
Small cell carcinoma	1	1	100	1	1	100
Giant cell carcinoma (incl. spindle cell ca.)	5	2	40	2	1	50
Small cell and giant cell carcinoma (together)	6	3	50	3	2	67
Totals	42	23	55	19	11	58

TABLE VI

FIVE AND TEN YEAR SURVIVALS (ACCORDING TO PORTMANN'S CLASSIFICATION)

Group	No. of Pts. Treated more than 5 Yrs. ago	5-Yr. Survivals No.	5-Yr. Survivals Per Cent	No. of Pts. Treated more than 10 Yrs. ago	10-Yr. Survivals No.	10-Yr. Survivals Per Cent
I	14	12*	86	8	6*	75
II	3	2	67	1	1	100
III	17	7	41	8	4	50
IV	9	2	22	3	0	0
Unclassified	1	0	0	..	..	..
Totals	44†	23	52	20‡	11	55

* Only one death among the patients in GROUP I is attributable to the thyroid carcinoma.

† 41 of these 44 patients have been followed. Two patients are included, on whom pathologic material is not available.

‡ 19 of these 20 patients have been followed. One patient is included, on whom pathologic material is not available.

In our experience, as presented in Table V, the pathologic classification of a thyroid carcinoma has a limited bearing on the prognosis. On the other hand, the end-results in the early cases (GROUPS I and II—Portmann) are strikingly better than in the more advanced cases (GROUPS III and IV—Portmann), regardless of tumor type (Table VI). It should be noted, however, that the

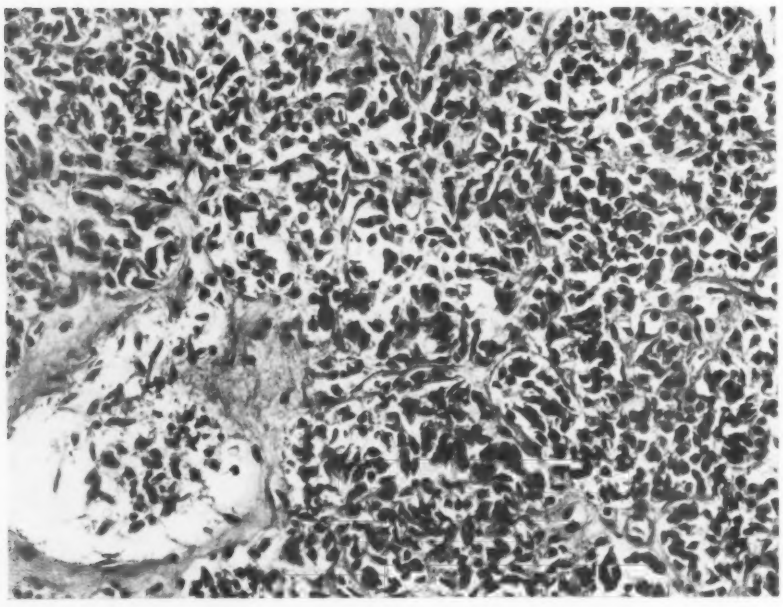


FIG. 2.—Small cell carcinoma of thyroid. The patient, a 19-year-old male, is alive and well, ten years after surgical removal and postoperative radiation.

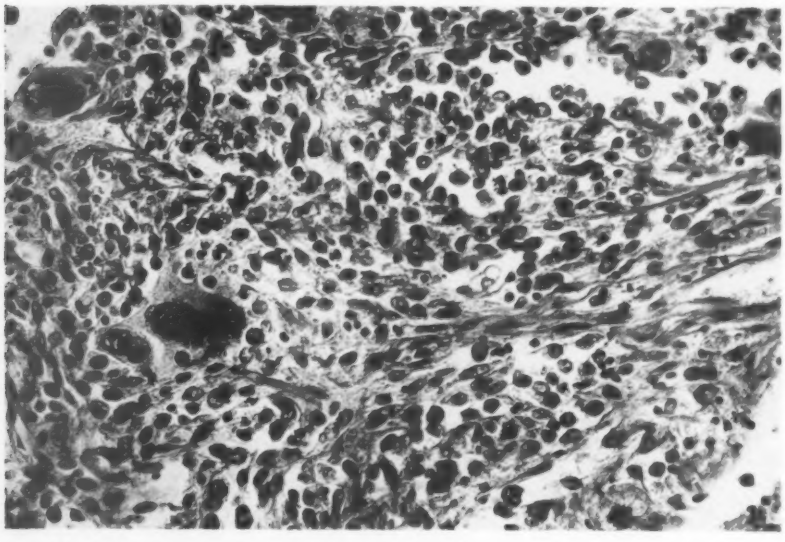


FIG. 3.—Giant cell carcinoma of thyroid. The patient, a 54-year-old female, is alive and well, ten years after surgical removal and postoperative radiation.

last two groups include a significantly greater number of patients over 50 years of age than do the first two groups (Table III) and that, therefore, the patients in GROUPS III and IV have a shorter life-expectancy regardless of the advanced state of their thyroid carcinomas.

Among the deaths occurring in GROUP I cases, only one could be attributed directly to the thyroid carcinoma. One patient with a malignant adenoma died after four years, with an independent primary carcinoma of the gallbladder; one with an adenocarcinoma after six years of a "stroke"; and the third, who had a papillary carcinoma, after nine years with a large gastric ulcer and renal decompensation. At the time of death none of these three patients had evidence of recurrence or metastasis of the thyroid carcinoma. One patient is alive, with metastases, seven and one-half years after operation. At five years she had been asymptomatic.

Many authors, notably Ward,[21] and Portmann,[17] among those who recently have written on the subject, have emphasized the tremendous importance of the extent of the disease in determining the prognosis. The experience of Rosh and Raider,[18] as well as our own, further supports this view.

POSTOPERATIVE RADIATION

Approximately one-half of the patients in GROUP I (Portmann,[17] Table VII) received postoperative radiation, whereas almost all of those in the other groups were so treated. Exceptions among the latter were, for the most part, patients who died before treatment could be instituted or before more than minimal amounts of radiation could be administered. The series, exclusive of the cases in GROUP I, includes 11 five-year survivals and five ten-year survivals. All but one of these patients received radiation. Our series does not include an adequate group of patients in Portmann's GROUPS II, III and IV who did not receive radiation to be used as a control series. In view of the character and extent of the lesions in these patients, the results obtained with operation and radiation were much better than had been anticipated. The prolonged survival of certain patients in whom the carcinoma could not be entirely removed, as judged grossly, leaves little doubt of the effectiveness of radiation.

TABLE VII

COMPARISON OF THE GROUP I SURVIVALS, WITH AND WITHOUT RADIATION

	No. of Pts. Treated more than 5 Yrs. ago	5 Yr. Survivals		No. of Pts. Treated more than 10 Yrs. ago	10-Yr. Survivals	
		No.	Per Cent		No.	Per Cent
With radiation therapy.....	7	7	100	5	4	80
Without radiation therapy...	7	5	71	3	2	67

The patients in GROUP I include three who died of unrelated conditions, without evidence of recurrence or metastasis of the thyroid tumor and one nonirradiated patient (not counted as a survival) who has been lost to follow-up. Thus, this group included only one case who is known to have died of

thyroid carcinoma within ten years. This patient was treated postoperatively by irradiation, but it is to be noted that her tumor was of the highly malignant spindle cell type.

In addition, one patient who survived ten years subsequently died with metastases, and another patient has developed a metastasis in the sacrum after seven and one-half years of freedom from clinical evidence of disease. Neither of these two patients received roentgenotherapy.

When one takes the pathologic classification into consideration, comparisons between radiated and nonradiated cases are possible only with the least malignant types. Our series includes nine five-year survivals and five ten-year survivals among patients with tumors classified as adenocarcinomas or giant cell, small cell or spindle cell carcinomas, but all of these patients were radiated, with the single exception of the ten-year survival, already mentioned, who subsequently succumbed to her disease. Table VIII compares the results with and without roentgenotherapy in the papillary carcinomas and malignant adenomas.

TABLE VIII

THYROID CARCINOMAS OF LOW OR POTENTIAL MALIGNANCY

	No. of Pts. Treated more than 5 Yrs. ago	5-Yr. Survivals No.	5-Yr. Survivals Per Cent	No. of Pts. Treated more than 10 Yrs. ago	10-Yr. Survivals No.	10-Yr. Survivals Per Cent
Malignant Adenomas:						
With radiation therapy....	8	4	50	2	1	50
Without radiation therapy.	5	3	60	2	1	50
Papillary Carcinoma:						
With radiation therapy....	6	5	83	4	3	75
Without radiation therapy.	5	2	40	2	1	50
Total:						
With radiation therapy....	14	9	64	6	4	67
Without radiation therapy.	10	5	40	4	2	50

TABLE IX

THYROID CARCINOMAS OF INTERMEDIATE AND HIGH DEGREES OF MALIGNANCY

	No. of Pts. Treated more than 5 Yrs. ago	5-Yr. Survivals No.	5-Yr. Survivals Per Cent	No. of Pts. Treated more than 10 Yrs. ago	10-Yr. Survivals No.	10-Yr. Survivals Per Cent
With radiation therapy.....	17	9	53	8	4	50
Without radiation therapy...	3	1	33	2	1	50

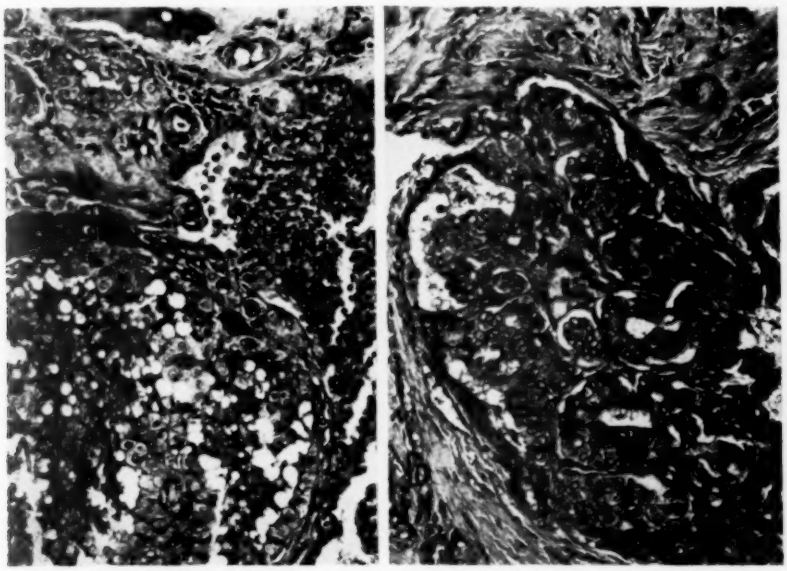
The figures in Table VIII suggest that benefit is more likely to be obtained from radiotherapy in the papillary carcinomas than in other types, a point which is in agreement with general experience of others.

Table IX compares the results with and without radiation in the more malignant tumors. The differences are not statistically significant. The number of cases is small, and it must also be remembered that the advanced cases with a poor, or hopeless, prognosis were usually given roentgenotherapy.

These data support the opinion of Portmann that routine postoperative roentgenotherapy does not clearly benefit the patient with a malignant adenoma or papillary carcinoma of the thyroid which has been discovered only on pathologic examination and which is confined within a capsule. However, our clinical observations lead us to believe that all other cases should receive radiation therapy.

LATERAL ABERRANT THYROIDS

During the 11.5 years covered by this report we have encountered four lateral aberrant thyroid tumors. The subject of lateral thyroid tumors has been thoroughly discussed by Frantz, and her associates,[4] and by Clay and



A B

FIG. 4.—(A) Papillary carcinoma of lateral aberrant thyroid.
(B) Carcinoma of the main thyroid gland of same patient, a 22-year-old male.

Blackman.[2] One of the lateral thyroid lesions in our series was benign but the other three were malignant, and all were predominantly papillary, with multiple lateral cervical nodules. The three patients with carcinoma were all males, age 19, 22 and 39, respectively. All are living without symptoms following surgical removal and roentgenotherapy, but they have all been treated within the past three years.

One patient in this group was the subject of radical neck dissection, during the course of which the homolateral lobe of the thyroid gland was resected. The operating surgeon (J. E. R.) was not aware of any suspicious lesion in the lobe but, nevertheless, a small carcinoma was detected on pathologic examination (Fig. 4). The main thyroid glands of the other two patients have not been removed, or explored, surgically, but neither patient presents clinical

evidence of involvement of the main gland as yet. Clay and Blackman[2] believe that the so-called lateral thyroid tumors are all metastases from occult carcinomas of main thyroid gland. Frantz, and her associates,[4] on the other hand, are convinced of the origin of these tumors in aberrant thyroid tissue, despite a frequent association with carcinoma in the main gland, which they consider to be independent. Our experience with these lesions is too small to permit us to draw any conclusions on this point but, since collecting this series, we have observed two additional patients with multiple, malignant lateral cervical thyroid tumors. Although the thyroid glands of these patients appeared normal at surgical exploration, lobectomies were performed, and small carcinomas were found in both cases. This limited experience lends some support to the contention of Clay and Blackman,[2] and of King and Pemberton,[12] that the so-called lateral aberrant thyroid carcinomas are, in reality, metastases from tumors of the thyroid gland.

The two patients who have not had thyroidectomies have done well. Both have had roentgenotherapy. The follow-up is still much too short to permit of accurate evaluation. In the case of the 19-year-old boy, the tumor was considered inoperable at a second operation for removal of recurrent or newly-developing nodules. Following intensive radiation, however, surgical removal was readily accomplished at a later procedure. The 39-year-old patient had a somewhat similar experience. He developed new or recurrent nodules within five months of the operative removal of the tumor observed originally. These were very extensive and complete removal was impossible. Following radiation this patient has remained without clinical evidence of thyroid or lateral thyroid disease for three and one-half years.

RADIOLOGIC CONSIDERATIONS

Fifty-two of the 71 patients in this group received radiation therapy. The records of 50 are complete with respect to technical factors and dosage.

Although the treatment was modified to meet individual requirements, most of the patients were treated at 200kv., 15ma., 0.5 mm. of copper and 1 mm. of aluminum filtration added, and 50 cm. T.S.D. Three portals were commonly directed to the neck; each lateral and an anterior portal, with a posterior portal sometimes added. The portals usually measured 10 x 13 cm. or 15 x 16 cm.

Most of the patients were given from 1,500 to 2,000 air roentgens to each portal in daily amounts of 200 air roentgens to one or two portals. The average total dose to the neck was about 5,000 air roentgens. Larger doses were given in several series. At present, our policy is to wait at least 2 to 3 months following surgery before beginning radiation therapy in order to permit physiologic repair to take place. If the surgical procedure is limited to a simple exploration and biopsy, irradiation is instituted immediately.

The average total dose to the neck among those patients who have survived five years, or more, was about 6,000 air roentgens. The smallest dose in this group of five-year survivors was 4,896 air roentgens.

In the group of lateral aberrant thyroid carcinomas, all three have received radiation therapy. Similar technical factors to those above were employed and the total dosage was 2,000 to 3,000 air roentgens to each of two or three portals.

Two patients with bony metastases were treated over the involved areas, and one showed recalcification of the lesion after 1,000 to 1,500 air roentgens had been given to two portals, while the other showed no recalcification after 1,000 to 2,500 air roentgens had been given to three portals. One patient with pulmonary metastases showed definite clinical and roentgenographic evidence of improvement after 1,200 to 1,600 air roentgens to anterior and posterior portals, respectively.

Our dosage to the primary tumor is quite similar to that of Hare's[8] who attempts to give 6,000 roentgens to the tumor bed. This amount, he believes, is close to the lethal tumor dose. He, however, begins therapy five or six days after operation because he has observed two cases who developed evidence of recurrence within two weeks after operation.

In none of our patients has there been any delay in wound healing. Mucositis usually developed after 12 to 14 days of treatment. The external skin reaction reached a maximum after about a month.

One of our patients presented an interesting problem in the management of pulmonary metastases. The roentgenologic examination of the chest revealed increased prominence of the lymph nodes in each hilum and an increase of the prominence of the lung markings in the right upper lobe, which was regarded as evidence of metastasis. Approximately 4,000 air roentgens were given to each of four portals directed toward the mediastinum. This resulted in a tissue dose of 3,698r to the center of each lung. Two months later the patient returned with dyspnea and cough following a cold. A roentgenogram at this time showed bilateral pneumonitis, and the possibility of radiation pneumonitis was considered. The patient's course continued downhill in spite of medical measures to combat infection, and he died. At autopsy, in addition to metastatic involvement of the hilar lymph nodes, a very firm infiltration of the right upper and left lower lobes was found. Histologic examination revealed radiation pneumonitis and metastatic carcinoma. We believe that the presence of metastatic carcinoma in this patient's lungs rendered him especially susceptible to radiation pneumonitis, and we would advise treating such patients with extreme caution.

SUMMARY AND CONCLUSIONS

Seventy-one cases of carcinoma of the thyroid and three of lateral thyroid carcinoma treated at the Hospital of the University of Pennsylvania during an 11.5-year period have been reviewed. Sixty-two thyroid cancers were encountered among a series of 2,079 surgically-treated thyroid lesions, an incidence of 3.0 per cent. This is an incidence of 5.4 per cent of carcinoma in 1,135 surgically treated *nodular* goiters.

Although the age-incidence is not greatly different from that of carcinoma

of other organs, the thyroid carcinomas occurring in the younger age-groups tend to be of the less malignant pathologic types and to be less advanced in their growth when they first come under observation.

A majority of thyroid carcinomas are of the papillary or malignant adenoma types, which may be grouped together as GRADE I tumors, or tumors of low or potential malignancy. Fifty-eight per cent of the patients treated for tumors of these types more than five years ago, and 60 per cent of those treated more than ten years ago are alive and well. Although the prognosis in tumors of other pathologic types is poorer, the ten-year survivals in our series include one patient with a small cell carcinoma and one with a giant cell carcinoma.

So far as prognosis is concerned, the extent of the disease at the time treatment is instituted is more significant than the pathologic type. Eighty-six per cent of the patients whose tumors were discovered only on pathologic examination, and who were treated more than five years ago, are alive and well. Seventy-five per cent of such patients treated more than ten years ago are alive and well.

Many patients with thyroid cancer develop metastases or recurrences five years, or more, after their initial treatment. This series includes one patient who died with metastases more than ten years after thyroidectomy.

In view of the relatively small risk of operation, it would appear wise to recommend the surgical excision of all nodular goiters unless strong contraindications exist. If carcinoma is present and extends through the capsule of the gland, postoperative radiation should be instituted. It has been especially effective in the papillary carcinomas. The benefits of postoperative radiation in cases in which the carcinoma has not extended through the capsule are not clear from the present study. So many of these patients do well that a considerably greater experience will be required before postoperative radiation in this group of cases can be finally evaluated.

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PRIMARY CARCINOMA OF THE LUNG, WITH INVASION OF THE RIBS

PNEUMONECTOMY AND SIMULTANEOUS BLOCK RESECTION OF THE CHEST WALL

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CLINICAL REPORTS have directed little attention to the incidence, behavior, and treatment of carcinoma of the lung invading the bony thorax, and such extension has been accepted generally as a contraindication to curative surgical attempts.[2, 3, 9, 11] The purpose of this communication is to question the relegation of these patients to an incurable group and to emphasize a method of treatment based upon sound principles of cancer surgery.

The incidence of bony thorax invasion is probably between five and ten per cent of all patients with carcinoma of the lung. Pathologic studies[5, 6, 7] have not only pointed out the frequency of chest wall invasion, but have emphasized the behavior of the cell type in relationship to rib erosion. In Koletsky's[5] study, five, or 8.3 per cent, of the 40 patients with squamous cell carcinoma of the lung showed an associated rib destruction, and this observation was confined to this cell type. A histologic diagnosis of primary cancer of the lung was made in 88 consecutive cases during the past eight years by the author. Seven patients, or 8 per cent, showed invasion of the chest wall, characterized by rib destruction in six cases.

The relationship of the cell type of carcinoma of the lung to erosion of the ribs or vertebrae is striking; however, there is a paucity of literature in attempting to confirm this correlation. The majority of so-called Pancoast[8] tumors are carcinomas of the lung. These tumors have as one clinical feature the local and adjacent destruction of a rib, and it was of interest to review the cell types of some of the published cases. Stein[10] reported 27 cases of malignant lesions in the region of the pulmonary apex, so-called superior pulmonary sulcus tumors. In nine bronchogenic carcinomas in which the cell type was determined, six were of the squamous cell variety and three were classified as adenocarcinomas. Habein and Miller[4] were able to collect, in 1938, a series of 27 reported cases fulfilling the requirements for a diagnosis of a Pancoast tumor. The cell type was given in 19 tumors, and in 14, where the bronchogenic origin seemed most probable, the squamous cell variety accounted for ten, adenocarcinoma two, medullary carcinoma one, and undifferentiated carcinoma one. Five of the 100 patients with carcinoma of the lung studied at autopsy by Koletsky[5] showed rib destruction, and in each instance the squamous cell type of tumor was present. In my series of 88 histologically proved carcinomas of the lung, the incidence of the squamous cell variety was 47 per cent, adenocarcinoma 24.1 per cent, and small cell carcinoma 28.9 per cent. The cell type was unclassified in five cases. The six cases showing invasion and destruction of a rib or ribs were of the squamous cell type. One

adenocarcinoma showed pericostal invasion of the soft tissue of the chest wall, but there was no osseous extension of the tumor. In our study of cases, 15.4 per cent of the squamous cell variety of lung cancer invaded the ribs, and this behavior was limited to this cell type. Squamous cell carcinomas of peripheral bronchogenic origin constitute the majority of primary lung tumors characterized by invasion of the chest wall with rib destruction.

The behavior of peripheral squamous cell carcinomas is not unlike the more centrally placed tumors of this type. This variety of tumor invades contiguous structures, infiltrates, grows slowly and metastasizes late in the course of the disease. In 100 postmortem examinations, Koletsky[5] found no extrathoracic dissemination in 65 per cent of the 40 cases with the squamous cell type. Olson[7] found regional node metastasis in 55 per cent and no nodal involvement in 14 per cent of 27 squamous cell carcinomas studied at autopsy. The behavior of this cell type is well-appreciated clinically. Thirteen of the 14 surviving patients in Adams[1] series of 49 pulmonary resections belong to the squamous cell group. In my series of 88 patients with carcinoma of the lung, it was possible to undertake a curative resection in 17, and of this group eight were of the squamous cell variety.

Although extension of carcinoma of the lung to the bony thorax is indicative of a well-advanced lesion, it is not indicative of a hopeless situation. If the local lesion can be excised with a healthy margin of soft tissues and bony thorax, the prognosis is favorable. In four cases accompanied by rib destruction, Koletsky[5] found no metastasis to the regional nodes at autopsy. In the six patients herein reported, there was no extension to the regional nodes.

Primary carcinoma of the lung accompanied by rib destruction in the majority of instances is due to the squamous cell type of tumor. The favorable pathologic behavior of this cell type lends itself well to radical cancer surgery. This has prompted the following case reports.

CASE REPORTS

Case 1.—C. C., a 40-year-old white female, had an 11 months' history of pain in the right chest unaccompanied by cough or other symptoms suggesting pathology of the right lung. The pain did not radiate down the right arm but remained localized to the right side of the chest. The pain was described as being of a sharp and "tearing" character, and for two months prior to her hospital admission morphine had been used daily to alleviate this symptom. The past history did not contribute any pertinent information, and the family history was irrelevant.

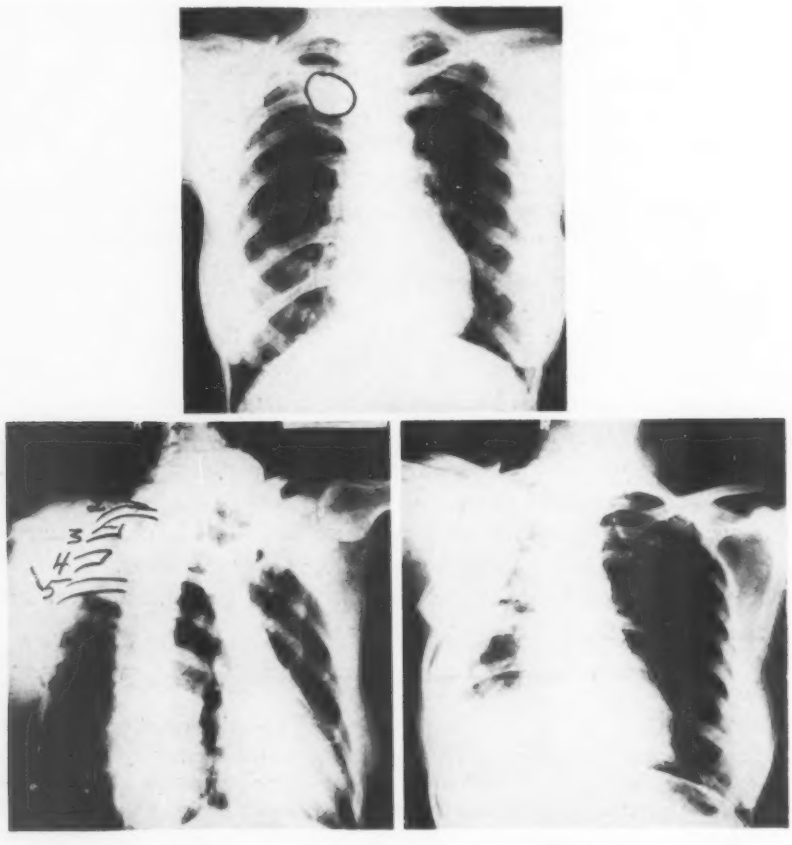
Physical Examination: The patient was having acute pain. Tenderness was present over the third rib adjacent to the spine. No other physical findings of pathology were present. The routine laboratory studies were negative. Roentgenologic examination of the thorax revealed a right apical tumor mass adjacent to the spine. The diagnostic bronchoscopy was negative and the right upper lobe orifice did not appear to be retracted upward. A diagnostic pneumothorax revealed a tumor mass involving the right upper lobe and the adjacent thoracic wall (Fig. 1). The third rib was partially destroyed adjacent to its respective transverse process.

Operation.—February 2, 1940: A right upper lobe lobectomy was performed, removing a block of the chest wall with the specimen. Posteriorly, the second, third, fourth and fifth ribs and their respective transverse processes were divided. The neurovascular

bundles were ligated. The ribs and intercostal bundles were divided in the anterior axillary line. The tumor mass had invaded and destroyed the head of the third rib and the tip of the third transverse process. There was no metastasis present in the mediastinal nodes.

Pathologic Report: Squamous cell carcinoma of the lung with osseous invasion of the third rib and transverse process.

A



B C

FIG. 1.—(A and B) Case 1: Routine and overexposed roentgenograms showing destruction of 3d, and 4th ribs adjacent to transverse processes.

(C) Postoperative roentgenogram showing upper lobe lobectomy and block excision of chest wall.

Postoperative and Late Course: On the 21st postoperative day this patient was discharged from the hospital, after an uneventful convalescence. She was entirely symptom-free for a period of eight months. At this time the patient complained of pain in the region of the third dorsal vertebra and one month later a paraplegia developed at this level. She grew progressively worse and died 11 months after the pulmonary resection.

Autopsy: There was no evidence of metastasis to the hilar lymph nodes. There was a local extension of the tumor which could not be removed at the time of the operation. Extensive invasion of the third dorsal vertebra and spinal cord was evident.

COMMENT: This was a palliative lobectomy, with simultaneous block resection of the chest wall. When such tumors invade the vertebrae a curative resection would appear impossible.

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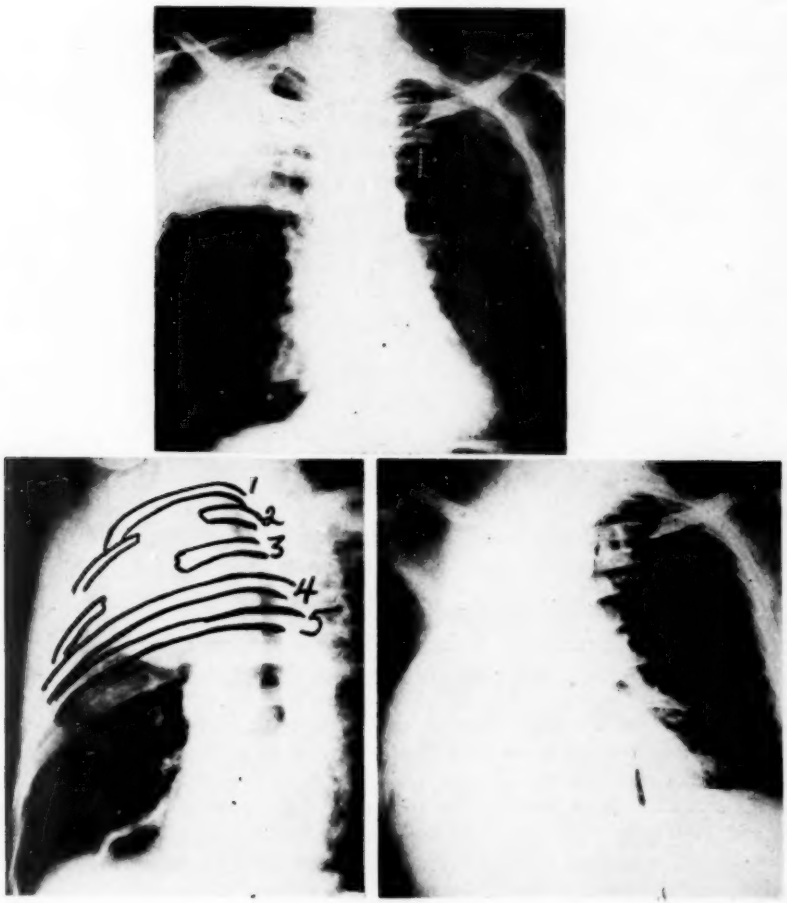

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FIG. 2.—(A and B) Case 2: Routine and overexposed roentgenograms showing a large peripheral squamous cell carcinoma of the lung, with destruction of the 2d and 3d ribs. Note in (A) the clear zone between the mesial border of the tumor and mediastinum.
(C) Routine roentgenogram of chest six years after operation.

Case 2.—J. B., a 55-year-old white male, had a nine months' history of pain in the right chest. The pain was severe in character and localized to the right infraclavicular region. Three months prior to his hospital admission he developed hemoptysis, and consulted a number of physicians relative to this complaint. During the ensuing three

months he lost 20 pounds in weight, and dyspnea became a troublesome symptom. The past history and family history were not significant.

Physical Examination: This examination revealed all the positive findings to be limited to the chest. Deep inspiration exaggerated the pain in the right chest, which corresponded to the distribution of the third intercostal nerve. There was an inspiratory lag on the right. Tenderness over the third rib posteriorly was elicited by percussion. Dullness was present in the right scapular region and high in the right axilla. The breath sounds were decreased in these two locations. No neurologic signs were present. The routine laboratory tests were within the range of normal.

Roentgenologic examination revealed a tumor mass in the dome of the right thoracic cavity. Overexposed films showed partial destruction of the second and third ribs (Fig. 2). A bronchoscopic examination revealed partial fixation of the right upper lobe bronchus. No intralumenary tumor mass was visible. Preoperative pneumothorax demonstrated fixation of the lung, tumor mass and chest wall. *Preoperative Diagnosis:* Squamous cell carcinoma of the lung.

Operation.—January 4, 1941: A right total pneumonectomy and block excision of the chest wall were carried out through a posterior approach. It was possible to cut through healthy tissue of the chest wall posteriorly and anteriorly to the tumor mass. The block of chest wall consisted of the second, third, fourth, fifth, sixth and seventh ribs and their respective intercostal bundles. The intercostal vessels were ligated close to the transverse processes and in the anterior axillary line.

The postoperative course was uncomplicated, and he was discharged from the hospital on the 25th postoperative day.

Pathologic Report: Grade 4 squamous cell carcinoma of the lung showing invasion and partial destruction of the second, third, fourth and fifth ribs. The regional nodes showed no metastasis.

Late Course: During the past six years, this patient has remained entirely well. There is no evidence of recurrence. He has a cough, but a recent bronchoscopic examination revealed a marked displacement of the trachea to the right and a smooth, well-healed bronchial stump. The cough appears mechanical in origin. A soft and yielding chest wall interferes somewhat with an effective cough.

COMMENT: An extensive squamous cell bronchogenic carcinoma invading the second, third, fourth and fifth ribs, has been apparently cured by a right pneumonectomy, with simultaneous block excision of the chest wall.

Case 3.—During the early part of December, 1942, F. P., a white male, age 41, developed pain in the right shoulder and axilla. Extraction of two teeth for apical abscesses did not relieve the pain. Six weeks of daily physical therapy seemed to exaggerate his symptoms. One month after the onset of pain, he developed a nonproductive cough, and, in March, 1943, the cough was associated with a blood-streaked sputum. One month prior to his hospital admission, he felt as if he were growing weaker, and he was somewhat short of breath. He had lost 15 pounds in weight.

Physical Examination: He appeared chronically ill. The skin was pale and dry. The positive physical findings were limited to the chest. Tenderness was present over the right scapular region. Dullness to percussion and suppression of the breath sounds were present in this region. There were no positive neurologic findings and no evident extrathoracic extension of a possible tumor of the lung. The routine laboratory work was within normal limits. Roentgenologic examination showed the apex of the right lung to be obscured by a dense opacity measuring 6.5 cm. in diameter. The mass lay posteriorly and extended into the costovertebral gutter. Overexposed films revealed partial destruction of the second rib posteriorly (Fig. 3). The preoperative diagnosis was squamous cell carcinoma of the lung.

Operation.—May 15, 1943: A posterolateral incision was made, entering the right

pleural cavity through the seventh intercostal space. A large tumor mass replaced the apical one-half of the right lung and had invaded the second, third, fourth and fifth ribs. Resection seemed feasible, in that disarticulation of the ribs accompanied by partial resection of the transverse processes would encompass the tumor and permit block excision through healthy tissue. The first, second, third, fourth, fifth, sixth and seventh ribs were treated in this manner posteriorly and then divided in the midaxillary line. This left attached to the tumor mass and right lung the seven ribs and their respective intercostal bundles. A right pneumonectomy was then carried out. He withstood the operative procedure satisfactorily, and at no time was he in any particular danger.

FIG. 3.—Case 3: Overexposed roentgenogram revealing a peripheral squamous cell carcinoma of the lung, with destruction of the 2d rib.

Twenty minutes after completion of the operation, the blood pressure was not obtainable in the arms. Such a marked change could not be explained on the basis of blood volume loss, for adequate blood replacement, 2,500 cc. of citrated blood, had been given; however, it was soon discovered that his blood pressure was normal in his legs and absent in the arms. A marked vasospasm following trauma and dissolution of the right sympathetic trunk was then considered as a possible etiologic factor. Papaverine effected an immediate response, and the blood pressure level in the arms returned to 100/70. This return of a satisfactory blood pressure level was delayed for approximately ten minutes, for the apparent disturbing factor was not recognized. During the ensuing 32 hours, this patient temporarily regained consciousness; however, he developed intermittent generalized convulsions associated with a variable pulse rate and blood pressure.

The respiratory exchange of the left lung was good. The convulsions were controlled by 25 per cent magnesium sulfate solution intravenously. The clinical picture was that of a decerebrated animal. The rectal temperature gradually rose to 108°F., and death occurred approximately 39 hours postoperatively.

Autopsy: The specimen of lung and adherent seven ribs revealed partial destruction of the second, third, fourth and fifth ribs by a Grade 4 squamous cell carcinoma of the lung. The regional nodes removed at operation were free of metastasis.

The findings at postmortem revealed, grossly, no cause of death. The left lung was normal. There was no evidence either grossly or microscopically of residual carcinoma. Examination of the brain revealed findings compatible with cerebral asphyxia. *Cause of Death:* Encephalopathy, secondary to asphyxia.

COMMENT: This was an advanced squamous cell carcinoma of the lung with erosion of multiple ribs, apparently curable by radical surgery. Cerebral asphyxia secondary to marked vasospasm involving the arms, neck and head seemed the most likely cause of death. A good oxygen concentration was maintained throughout the operative procedure. The photo-electric cell revealed a 90 per cent, or better, oxygenation of the blood. The ten-minute postoperative period, characterized by absent blood pressure in the arms with a normal blood pressure in the legs, was probably sufficient to produce irrevocable brain damage.

Case 4.—T. H., a 41-year-old white male, a painter by occupation, had a history of recurrent pain in the right shoulder for a period of two years. The pain was exaggerated by damp weather and by persistent use of the right arm. Four months prior to his admission to the hospital, he developed an entirely different type of pain which was sharp, shooting and burning in character. This pain would radiate from the right shoulder to the midline of the chest. Sudden jolting movements of the right shoulder would initiate the pain in the right chest, and for two weeks he avoided use of the arm. He had no cough and no shortness of breath.

The past history revealed that he had a fracture of the left humerus in 1938, at which time he had pain in the right shoulder. His mother and paternal grandfather died of cancer. The remaining history did not contribute any findings of importance.

The physical examination was essentially negative throughout. He was a fairly well-nourished man of small stature. The routine laboratory studies were negative.

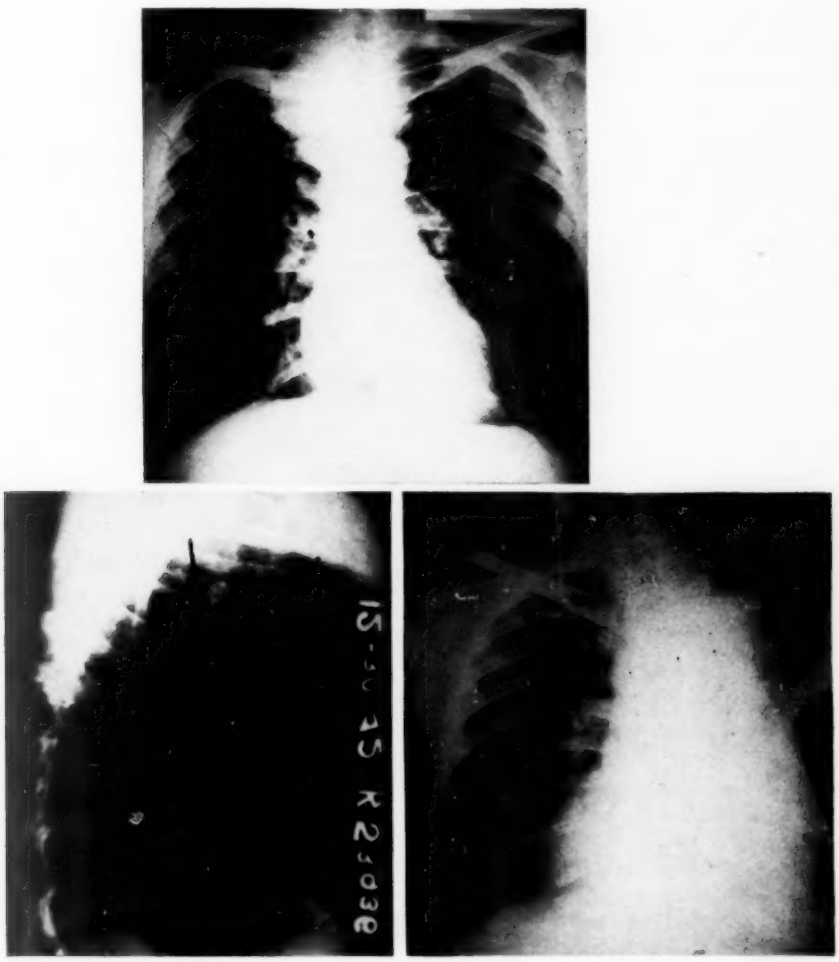
Roentgenologic examination revealed a circumscribed area of increased density in the middle one-half of the right apical and subapical region of the lung. The total area of involvement measured six centimeters in diameter. In the lateral view there was a circumscribed shadow of slightly increased density in the mediastinal region measuring three centimeters in diameter (Fig. 4). This produced a wedge-shaped density quite characteristic of a lobular atelectasis. Bronchoscopic examination was negative and there were no secretions arising from the right upper lobe orifice. *Clinical Diagnosis:* Bronchogenic carcinoma of the upper lobe of the right lung.

Operation.—February 2, 1943: A total pneumonectomy was carried out on the right for a carcinoma involving the apex of the right lung and infiltrating the soft tissue of the chest wall. A frozen-section diagnosis of the soft tissue removed from the third interspace confirmed the clinical suspicion of invasion of the chest wall. Following removal of the right lung, a block resection of the chest wall was carried out removing the second, third, fourth, fifth and sixth ribs. The intercostal bundles were ligated adjacent to the transverse processes posteriorly, and anteriorly the bundles were divided in the anterior axillary line.

The pathologist reported bronchogenic adenocarcinoma of the lung, Grade 3, upper lobe bronchus right lung, with soft tissue extension to the chest wall. The regional nodes were not involved by metastasis.

The postoperative course was uneventful, with the exception of the development of a small residual empyema which was drained on March 4, 1943. The empyema cavity was unaccompanied by opening of the bronchus and rapidly decreased in size. Six weeks after drainage of the empyema, he returned to his home. He has been unable to return for follow-up examination.

A



B C

FIG. 4.—(A and B) Case 4: Routine PA and lateral roentgenograms of chest showing an apical tumor. Note the triangular area of atelectasis in the lateral film. (C) Routine roentgenogram six months after right total pneumonectomy and block excision of the chest wall.

COMMENT: This was an advanced adenocarcinoma of the right lung invading the soft tissue of the chest wall, unaccompanied by regional lymph node involvement. There was no associated rib destruction in spite of soft tissue involvement of the chest wall adjacent to the ribs.

Case 5.—T. J. was a colored male, age 42, who had a history of severe pain in the right shoulder and right side of the neck for a period of eight months. He had taken numerous drugs for the relief of pain without benefit, and two weeks prior to his admission to the hospital, the pain began to run down the inner aspect of the arm. He had been placed on morphine for the relief of pain. He had a cough for five months and a three months' history of repeated attacks of hemoptysis.

Physical Examination: The patient was undernourished, dehydrated, and in acute pain. There was ptosis of the right lid and myosis of the right pupil. There was an absence of sweating over the right side of the face. In the right supraclavicular region there was a mass measuring 1 x 2 cm. in diameter. This mass was freely movable and firm. The right arm was held close to the trunk and there was marked limitation of movement of the right shoulder. The pain radiated primarily down the inner aspect of the arm on motion. Tenderness was present over the suprascapular region on the right corresponding to approximately the first and second ribs posteriorly. Deep inspiratory movements exaggerated the pain in the right arm. There was a slight respiratory lag on the right. The percussion note was negative. The breath sounds were decreased in the right scapular region. The routine laboratory work was negative.

Roentgenologic examination revealed a tumor, measuring 4 x 6 cm., in the apex of the right lung adjacent to the spine. Overexposed films revealed destruction of the first and second ribs. Bronchoscopic examination did not seem to be indicated.

The clinical impression was squamous cell carcinoma of the upper lobe of the right lung with bony thorax and cervical sympathetic trunk extension. The tumor in the right supraclavicular region was removed surgically and showed a lymph node partially replaced by metastatic squamous cell carcinoma.

COMMENT: Advanced squamous cell carcinoma of the right lung with extension to the ribs and cervical sympathetic trunk.

Case 6.—M. R., a 64-year-old white male, and a salesman by occupation until the onset of severe pain in the right chest in June, 1939. The pain was exaggerated by coughing and by deep inspiratory efforts. Deep heat therapy and numerous remedies had been used for the relief of the pain. The pain was severe in character and radiated from the back around to the upper part of the abdomen. In February, 1940, he developed hemoptysis which persisted until the time of admission to the hospital on May 5, 1940. He had had a cough which was different from the customary "cigarette cough" for a period of six months. He had lost 15 pounds in weight and was short of breath on moderate exertion.

Physical Examination: The patient was an elderly white male, with acute pain in the right side of the chest. He described an area of tenderness and could easily point out its location in the midaxillary line. The examination was essentially negative with the exception of the chest findings. There was an area of localized tenderness over the sixth and seventh ribs in the midaxillary line, and pressure at this point reproduced the referred pain to the anterior abdominal wall. There was a respiratory lag on the right and the percussion note was altered in the region of the point of tenderness. The breath sounds were diminished over the lower lobe of the right lung. The routine laboratory studies were within the range of normal.

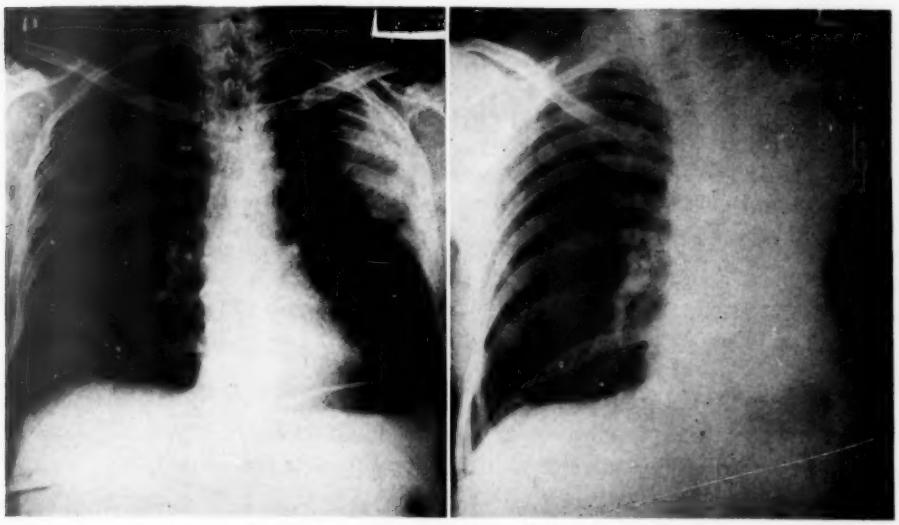
Roentgenologic examination revealed a 6 x 8 cm. mass involving the lower lobe of the right lung and partial destruction of the sixth, seventh and eighth ribs. A bronchoscopic examination revealed no evidence of an intralumenary tumor.

On May 9, 1940, a biopsy of the chest wall and partially destroyed eighth rib revealed squamous cell carcinoma apparently of bronchogenic origin.

This patient was discharged from the hospital two weeks after his admission and advised to take morphine for the relief of his pain. He lived for a six-month additional period during which time he had severe and persistent pain in the right chest.

Autopsy: A squamous cell carcinoma of the lower lobe of the right lung was identified. Extensive destruction of the sixth, seventh, eighth and ninth ribs was present; however, there was no metastasis to the regional lymph nodes. A bronchopneumonia involved primarily the right upper lobe and lower lobe of the left lung.

COMMENT: This extensive squamous cell bronchogenic carcinoma, associated with rib destruction, was operable and apparently curable at the time this patient presented himself for treatment. The author's experience in managing this type of patient suggested the likelihood of curability in such cases by a total pneumonectomy, with simultaneous block resection of the chest wall.



A B

FIG. 5.—(A) Case 7: Regular PA roentgenogram of chest showing large peripheral squamous cell carcinoma of the lung, left.
(B) Case 7: Postoperative roentgenogram showing block excision of chest wall and total pneumonectory, left.

Case 7.—C. L., a 53-year-old white male, a farmer by occupation, developed pain in the left chest in January, 1946. The pain radiated from the precordial region posteriorly to the midportion of the back. Pain had been persistent in character and there had been frequent exacerbations of severe pain which required narcotics for symptomatic relief. Soon after the onset of pain in January, he began to have attacks of hemoptysis. Dyspnea had not been a troublesome symptom, except during the attacks of severe pain.

Past History: He had had a chronic cough for 20 years, but there was no change in the cough until January, 1946. Six years prior to this hospital admission, he sustained a blow to the left chest which rendered him unconscious. Pain and soreness followed this injury, but he entirely recovered within a period of one month. He had pneumonia as a child which was complicated by a lung abscess. This healed without operative intervention. The family history is irrelevant.

Physical Examination: The patient was in a good state of nutrition. The positive findings of the examination were limited essentially to the chest. There was a respiratory lag on the left. Percussion note was dull high in the axillary region and over the left scapular region. Breath sounds were diminished and vocal and tactile fremitus were

increased in these regions. Tenderness to palpation was present over the fourth, fifth, sixth and seventh ribs in the midaxillary line. The heart sounds were of good tone and quality. Blood pressure was 116/78. Kidney function tests revealed normal findings. Roentgenologic examination revealed a ten-centimeter mass in the lateral one-half of the left chest extending from a level of the third rib to a level of the seventh rib in the posterior axillary line (Fig. 5). Overexposed films showed destruction of the fourth, fifth and sixth ribs in the posterior axillary line. *Clinical Diagnosis:* Squamous cell carcinoma of the lung, with invasion of the ribs. Bronchoscopic examination was not carried out in view of the peripheral location of the tumor.

Operation.—September 5, 1946: A total pneumonectomy on the left was performed, removing a block of the chest wall with the specimen. The second, third, fourth, fifth, sixth, seventh and eighth ribs were removed *en bloc*, dividing the ribs and neurovascular bundles posteriorly at their junctions with the transverse processes. The ribs and intercostal bundles were divided again at the anterior axillary line. This wide excision included the infiltrating tumor of the chest wall. During the operation 2,500 cc. of citrated blood were given.

Pathologic Report: Squamous cell carcinoma of the lung, with osseous invasion of the second, third, fourth, fifth, sixth and seventh ribs. The regional nodes showed no evidence of metastasis.

Postoperative and Late Course: This patient's immediate postoperative course was complicated by his inability to cough and expel pulmonary secretions. Extensive decostalization of the chest wall was responsible for his inability to cough. This complication was managed by five postoperative bronchoscopic aspirations and repeated intratracheal catheter suction. Ten days postoperatively, he was able to be up and about, and the pulmonary secretions could be evacuated with ease.

COMMENT: This was an advanced squamous cell carcinoma of the lung, with erosion of multiple ribs, apparently cured by radical surgery. Postoperative difficulty in evacuating secretions was again encountered in this patient.

SYMPTOMS AND DIAGNOSIS

Delay in diagnosis of this particular group of patients can be ascribed partially to the late manifestation of symptoms in carcinoma of the lung of peripheral origin. Pain preceded other symptoms, and it was of a severe character, persistent, and well-localized. Pain of months' duration often failed to direct attention to the possibility of a lung tumor. In the early stages, pain may be present, but the roentgenographic appearance may easily be overlooked. Other than pain, there are few symptoms until late in the course of the disease. Tenderness to percussion and palpation was present in each case and the rib or ribs invaded could be identified with ease.

Roentgenologic examination constitutes one of the best methods of diagnosis of either a peripheral or centrally-placed carcinoma of the lung. These cases reveal evidence of a peripheral, sharply cicumscribed, and dense tumor mass. In the early stages the tumor mass is small and may be overlooked. Rib destruction is revealed by overexposing the films, and this examination frequently underestimates the extent of bony destruction. Intrapleural pneumothorax adds little additional information. Direct biopsy of the invaded rib will establish a tissue diagnosis, but it carries with it the danger of soft-tissue implantation in apparently operable patients. Needle biopsy has the objec-

tionable features of seeding cancer along the needle track, hemorrhage, and infection. Bronchoscopy is not indicated, for the tumors are peripheral in location. Exploratory thoracotomy is the method of choice in select cases for determining the tissue diagnosis and operability. The pleural cavity is entered a rib and full rib's interspace below the lesion. In addition to determining operability; this site of approach facilitates the technical procedure of block excision of the chest wall and lung. Involvement of the brachial plexus, sympathetic trunk, phrenic nerve and the transverse processes of the vertebrae contraindicate curative surgical attempts, but a palliative resection must be considered in view of the associated severe pain. If the postero-anterior roentgenologic view of the chest delineates lung tissue between the mesial border of the tumor mass and mediastinum, local operability has been established. Invasion of the serratus anterior muscle is not a contraindication to block excision, for such occurred in one patient (Case 2), who has survived for a period of six years.

TREATMENT AND RESULTS

The successful treatment of cancer of the lung invading the ribs depends upon extirpation of the local lesion and regional lymphatics. This embraces block excision of the chest wall leaving a margin of healthy tissue attached to the involved structures, total pneumonectomy, and resection of the regional lymph nodes. Although radical excision of the chest wall accompanying pneumonectomy will probably increase the mortality rate in general for cancer of the lung, it seems of little importance when the prognosis of these patients subjected to block excision and pneumonectomy is considered. The pathologic behavior of the type of cancer of the lung invading the ribs makes it suitable to block excision and a good prognosis will eventually be established by further experience. The postoperative management of these patients is more difficult in that decostalization of the involved hemithorax renders the cough ineffective. Repeated catheter suction and frequent bronchoscopic removal of the secretions has been necessary in my experience.

Five of the patients herein reported were subjected to block excision of the chest wall and pulmonary resection. A total pneumonectomy was carried out in four, and a palliative lobectomy in one. There was one operative death. The patient with a palliative lobectomy died 11 months postoperatively. The remaining three patients are living and well, one for six years, one for two years, and one for five months.

SUMMARY

Invasion of the ribs by primary carcinoma of the lung is not uncommon. The symptoms and methods of diagnosis have been discussed. The cell type and favorable pathologic behavior of these tumors makes them amenable to radical cancer surgery. Successful treatment embraces block resection of the chest wall, total pneumonectomy and removal of the regional lymph nodes. Five of the seven cases herein reported illustrate this method of treatment.

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THE USE OF A MIXTURE OF PURE AMINO ACIDS IN SURGICAL NUTRITION*

I. CERTAIN PHARMACOLOGIC CONSIDERATIONS

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PART I

COX,[1] ELMAN,[2] AND OTHERS,[3, 4, 5] have shown that protein hydrolysates can replace protein for nutritional purposes. These materials have been extensively investigated clinically and certain practical difficulties in their use have become evident,[6] especially parenterally. The rate of intravenous administration is limited and the volumes required are large. To administer the equivalent of 90 Gm. of protein requires eight or nine hours and a volume of 2,500 cc. This tires the patient, prevents ambulation or may interfere with sleep. Febrile reactions, nausea and vomiting may occur. The material may be irritating subcutaneously. There is, thus, still a need for protein substitutes that can be given parenterally without these limitations.

Recently, Madden[7] has studied various mixtures of pure amino acids in respect to their efficiency in regenerating plasma protein in the dog subjected to plasmapheresis. One of these mixtures, VUJ† was found to be useful for this purpose and was tried in a patient, a man with chronic ulcerative colitis. Nitrogen retention was shown by the patient, and so, presumably, protein formation. It, therefore, seemed desirable to give this material an extended clinical trial. The results of this study are presented in this and the subsequent papers.

METHODS AND MATERIALS

First experiments were conducted with a 10 per cent solution of the amino acid mixture. Frequent spontaneous precipitation was noted upon refrigeration and made this solution unsafe for routine use. An 8 per cent concentration proved to be quite stable, providing a light, greenish-yellow, clear, bitter-tasting solution, which remained apparently unchanged for periods up to three months. This solution was given to most of the patients. A 5 per cent dextrose 8 per

* The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Columbia University.

† 65 Gm. of the VUJ mixture has the following composition:

dl-threonine	7.0 Gm.	dl-tryptophane	1.2 Gm.
dl-valine	9.0 Gm.	dl-phenylalanine	4.5 Gm.
l-leucine	10.0 Gm.	dl-methionine	4.0 Gm.
dl-isoleucine	7.0 Gm.	l-histidine HCl	2.6 Gm.
l-lysine HCl	8.0 Gm.	l-arginine HCl	5.2 Gm.
		glycine	6.5 Gm.

cent amino acid mixture was tried on 12 patients but was not used further because of nausea, vomiting or mild temperature rise in 10 of the 12 cases.

One liter of the 8 per cent amino acid solution provides about 9.6 Gm. of nitrogen. About 14 per cent of the amino acids in solution is dextrorotatory and may be considered to be unavailable for protein anabolism. There is also a loss of 1 to 5 Gm. of amino acid nitrogen by excretion as such into the urine, after the infusion of 1,500 to 3,000 cc.

The solution has a p_H of 5.5. Because of this acidity, 480 cc. of ⅙ molar sodium lactate solution were given to provide base when large amounts of the amino acids were used parenterally. A few trials were made intravenously of the amino acid solution after neutralization, but the material produced nausea or pyrexia after small amounts.

The 8 per cent material was employed in a total of 73 cases, some for periods up to three weeks and in amounts up to three liters per day. The usual method of administration was by infusion, and a total of about 350 infusions were given. The material has been given by hypodermoclysis in about 25 instances. Cardiac and renal function were evaluated before treatment and the fluids given through a venous pressure machine, when there was doubt. Varying rates of infusion of the amino acid mixture up to one liter per hour were tested. Blood CO_2,[8] chlorides,[9] urea nitrogen,[10] and hematocrit[11] were followed by standard methods when treatment was continued for several days. The infusions generally were the sole source of nitrogen, with intravenous or subcutaneous supplements of 1,500 to 3,000 cc. of a 5 per cent dextrose saline solution or occasionally of 480 cc. of ⅙ molar sodium lactate solution. In other instances, food was given but the amino acid solution was provided to supplement an inadequate protein intake. Amino acid blood levels were occasionally determined after infusion.[12]

RESULTS

Reactions: Nausea and vomiting were the only frequent ill effects of amino acid therapy. The occurrence of these symptoms appeared to be related to the rate and amount of administration. Amounts up to a liter per hour were given without reaction, but, in general, 400 cc. per hour was the maximum speed consistently tolerated. Women may tolerate the material less well, though few trials were made in women. Data concerning the blood level of amino acid at the time of nausea is incomplete. Seventeen patients were studied. The blood amino N. was elevated to between 9.6 and 25.8 mg. per cent, 1.5 to 2.5 hours following the start of the infusion. One value of 32.5 mg. per cent was observed. In general, nausea was found consistently with levels over 20 mg. per cent (four cases). The blood level was restored to normal by several hours after infusion so that the division of the desired dosage into morning and afternoon infusions frequently avoided symptoms.

Hyperpyrexia and chills occurred in five patients. In three of these, the same amino acid solutions were readministered without recurrence of fever. Pyrogenic reactions[13] to glucose and saline were noted at this time throughout the hospital, so that these reactions probably resulted from faulty care of the

infusion sets. In the other two cases, the amino acid mixture was administered during the course of a preëxistent fever and was followed by a chill and temperature rise lasting for many days. The reaction to the amino acid infusions may have been a coincidental flare-up of the original disorder, rather than a pyrogen response. In any event, the incidence of febrile reactions is low.*

Thrombophlebitis was not noted as a result of the amino acid infusions except where a Lindemann needle was left *in situ* for several days after operation. This maneuver produces venous thrombosis with dextrose or saline alone. Venous spasm of the smaller veins of the lower arm and hand occurred relatively frequently with infusions into these sites, prolonging the infusion time considerably.

Amino acids were given by hypodermoclysis in about 25 instances, 1,000 cc. per day. Cellulitis was noted once, although most of the patients began to complain of pain and tenderness during the treatment, especially after several clyses had been given.

The carbon dioxide content of the blood was reduced by the administration of more than 2,000 cc. per day of the amino acid solution and the fall was not prevented by the concurrent administration of 12 Gm. of sodium chloride as a 5 per cent dextrose-saline solution or by the use of 480 cc. of ⅙ molar sodium lactate solution. The impression was gained, however, that sodium lactate may have lessened the degree of fall. One death occurred associated with a drastic reduction in blood carbon dioxide content. The complete history is given below:

Case Report.—P. N., male, age 47, who underwent a partial gastrectomy and resection of a jejunal ulcer April 17, 1945.

The history was essentially irrelevant except for some weight loss of about 10 or 15 pounds prior to operation. Physical examination was negative. Prior to operation a glucose tolerance test showed a fasting blood sugar of 142; at .5 hour 170; 1 hour 206; and 2 hours 143, although it was 52 at 3 hours. On day 1 after operation, he received 1,500 cc. 5 per cent glucose and saline, with 2.5 Gm. sulfadiazine. This was repeated on day 2. On day 1, a urea nitrogen was 21 mg. per cent. CO_2 59.8 vols. per cent. Chloride 570 mg. per cent. On day 1, he received 1,500 cc. 8 per cent amino acids. On day 2, 3,000 cc. On day 3, 1,500, and day 4, 1,500. On day 3, urea nitrogen was 40, with a CO_2 of 20.2 and chlorides 662. This report was not received until after the amino acids was given on day 4. On day 5, he developed pulmonary edema, had a urine output of 190 cc., and a blood CO_2 of 16 vols. per cent, for which 40 Gm. of sodium bicarbonate was given. During the day his temperature rose to 104.8°F., and he died in 12 hours. At this time his urea nitrogen had fallen to 23 mg. per cent. Aside from acidosis and pulmonary edema, the cause of death is unknown. There was no autopsy.

* The admixture of glucose, or the neutralization of the mixture with alkali, appears to alter the property and toxicity of the solution. For this reason, dextrose-saline is not mixed with the amino acid solution, but precedes or follows it, or is given by a different route. Also, such substances as sulfadiazine, vitamins for parenteral administration, or other intravenous medications, are not added to the amino acid solution but rather to the dextrose-saline. The amino acid solution, like the hydrolysates, is an ideal medium for bacteria, so that any left-over solution must be discarded and not saved for later use, and the solution must not be allowed to stand open before use.

Aside from this case, the lowest value for blood CO_2 after 3,000 cc. infusion a day for three days was 24 vols. per cent, the average value about 40 vols. per cent. Twenty patients were treated for three to five days with daily infusions of amino acid solutions. The range of values of lowest recorded blood CO_2 levels was 16 to 57.9 vols. per 100 Ml. of blood. The corresponding range in six controls was 53.2 to 73.0 vols. per 100 Ml.

The values for the highest blood urea nitrogen were 10 to 40 mg. per cent in the treated patients and 13 to 26 mg. per cent in the controls. The urea nitrogen values are no higher than is found after the ingestion of much protein, or with gastro-intestinal bleeding.[14]

The Metabolism of Administered Amino Acids.—A rise in amino acid nitrogen in the urine was noted after infusion. Between 1 and 4 Gm. of amino acid nitrogen per 24 hrs. were lost in this form (Table I). The speed of

TABLE I

SHOWING EXTREME VALUES FOR AMINO ACID NITROGEN EXCRETION DURING FIRST WEEK AFTER OPERATION, AFTER 3 TO 5 DAYS TREATMENT WITH A MIXTURE OF PURE AMINO ACIDS

Patient	Amount of Infusion (cc.)	Urine Amino Acid Nitrogen (Gm./24 Hr.)
J. C.	2,000	2.42
J. D.	2,000	0.80
J. H.	2,000	4.16
W. H.	2,000	3.80
A. K.	1,000	1.72
C. M.	1,000	2.63
J. N.	2,000	3.0
W. R.	1,500–2,000	0.92
R. S.	2,000	3.02
E. C.	2,500	2.60
H. J.	2,500	2.34
A. Z.	2,500	1.90
E. J.	3,000	3.20
L. J.	3,000	2.38
P. W.	3,000	1.18
Control Cases		
F. Y.		0.56
M. O'R.		0.57
A. S.		0.52

infusion had little effect on this value. The great bulk of the amino acid was converted into urea as evidenced by a rise of urea nitrogen in the blood and the greatly increased urinary nitrogen. The rest was utilized to form protein as evidenced by nitrogen balance and by the nitrogen sulphur ratio. This is discussed in a subsequent paper.

DISCUSSION AND CONCLUSIONS

A mixture of the ten essential amino acids and glycine has been subjected to a clinical trial and can be readily administered. About three quarters of the nitrogen is l-rotatory and is physiologically available as may be part of the d-rotatory material.[15] A rate of administration of 400 cc. per hour appears to avoid any toxicity, at least in men, except in rare instances when nausea and

vomiting appear. Lowering of blood carbon dioxide content and rise in urea nitrogen occur with more than 2,000 cc. of the 8 per cent solution a day. The rise in urea nitrogen is no more than occurs with similar amounts of beef protein.[14] There is no evidence of renal damage[16] either in the urine or in delayed return of blood values to normal with stopping treatment.

An infusion of 1,500 cc. of this solution provides the average daily requirement of 15 Gm. of available nitrogen, about 95 Gm. of protein equivalent, and can be given in about four hours. About 350 calories are furnished, since most of the dextrorotatory, and presumably physiologically inactive, isomers are also burned. Caloric supplements must be given along with the amino acids, as food or as dextrose-saline solution. Fifteen hundred cubic centimeters of 5 per cent dextrose-saline solution provide 75 Gm. of sugar or 300 calories. Thus, 1,500 cc. of amino acid solution must be supplemented by a minimum of 3,000 cc. of 5 per cent dextrose-saline solution or dextrose in water, to give the patient a total of 950 calories, not counting the 1 to 4 Gm. of amino acid nitrogen which are excreted unchanged in the urine and so are lost for combustion purposes—about 80 calories.

It is feasible to give as much as 1,500 cc. of the amino acid solution twice daily to provide 28.8 Gm. of nitrogen; the amount of supplementary 5 per cent dextrose-saline is reduced to 1,500 cc. so as not to overload the circulation. Thus, a total of approximately 1,000 calories and the equivalent of about 180 Gm. of protein is given in 4,500 cc. The only apparent danger with the larger doses is the progressive fall in blood carbon dioxide content after several days of therapy and the rise in blood urea nitrogen. Emaciated patients who cannot afford to lose from their fat stores can only be treated for short periods by this technic to build up their body protein stores, unless some calories are taken by mouth. However, the still relatively well-nourished hypoproteinemic patient can build up protein in this way, at the expense of fat, for long periods, if the amino acids are used to supplement an inadequate food intake.

Again, mention should be made of the importance of the evaluation of cardiac reserve prior to therapy and of observation of the patient with limited reserve during infusion by means of vital capacity and venous pressure. It might be mentioned that at a rate of 400 cc. per hour even patients known to be on the border of failure have tolerated large amounts of amino acid without difficulty. In these patients the glucose supplement is given by clysis so that it will not be readily absorbed should signs of cardiac failure supervene. It should also be mentioned that amino acids should not be used when there is any indication of renal damage, in view of the acidosis and the rapidity of urea nitrogen accumulation in the blood which results even with normal kidney function. The one death in this series, however, cannot be explained by renal failure. Acidosis may have been responsible for the fatal outcome. Evidence of hypersensitivity was not noted although it is improbable that such reactions would occur with pure amino acids. Thus, the cause of death is obscure but may be related to the deaths reported with casein hydrolysates.

The above discussion has been chiefly limited to parenteral therapy. The availability of a compound which can replace or supplement dietary protein

intake by vein does not alter the fact that food is the best approach to adequate nutrition and should be given whenever possible. The protein in food is more efficiently utilized over long periods and provides at least some minerals and vitamins, as well as higher calories. However, if necessary, the amino acids provide an ideal supplement for an inadequate food intake and are most simply and efficiently used in this way.

As yet the use of the VUJ mixture of amino acids is limited by the high cost. A nontoxic hydrolysate of approximately the same composition would be equally suitable for nutritional purposes. However, if no such product becomes available, it is possible that an increased demand for this material will enable production costs to be reduced considerably.*

SUMMARY

1. A mixture of pure amino acids in 8 per cent solution has been given an extensive clinical trial, parenterally.

2. Few toxic effects have been noted with the 8 per cent solution. The incidence of nausea and vomiting, reduction in blood carbon dioxide content and urea nitrogen, and the excretion of unchanged amino acids is recorded.

3. The case report of one death of obscure origin, possibly from acidosis, is presented.

4. The available nitrogen and calories that can be given as pure amino acids is discussed and the use as a sole source of nitrogen or as a supplement to food is discussed.

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PART II

EFFECTS UPON NITROGEN BALANCE

IT IS WELL-ESTABLISHED that one of the results of injury to the body is the appearance of negative nitrogen balance on the same nitrogen intake which previously maintained equilibrium.[1-5] It is disputed as to whether an increase in the nitrogen intake will reëstablish equilibrium or whether new mechanisms make this impossible. Investigation of this problem is hindered by the poor appetite of the patients so that high nitrogen intakes are generally difficult to achieve. Recently, a mixture of pure amino acids[6] has become available and it has been possible to give reasonably large amounts of nitrogen parenterally with somewhat less difficulty than with protein hydrolysates.[7]* The results of this experience are presented here as is a concept of the mechanism responsible for the negative nitrogen balance after injury, suggested by these data.

METHODS

A metabolism ward set-up was established on one of the surgical floors of the Presbyterian Hospital. Special nursing and orderly care, a dietitian and diet kitchen for the project were provided. Urine, stools, gastric drainage and vomitus were collected in 24-hour amounts and analyzed daily for nitrogen.[8] Urines were preserved with chloroform in the ice chest, the other specimens under concentrated sulphuric acid. Urine creatine, creatinine and total neutral 17-ketosteroid determinations were done early in the study but were abandoned

* Dr. D. F. Robertson, of Merck and Co., generously supplied the solution of pure amino acids (VUJ) which made this study possible.

after it was established that correlation with the effects of operation was not significant. Urine total sulphate[9] and amino acid nitrogen excretion[10] were followed daily in most cases. Amino acid intake was determined by weighing the containers before and after administration. Food nitrogen intake was estimated by standard tables, with occasional check nitrogen determinations on samples of the diet. A casein hydrolysate† was used in some instances as a supplementary source of nitrogen and sugar. Most patients received a single transfusion of 500 cc. of blood after operation. This protein does not appear in the urine for a number of days[11] after transfusion, so the nitrogen involved was not entered into the balance calculations. Because of the transfusion and fluids given during operation, amino acid infusions were not begun until the day after operation, to avoid overloading the circulation. In the early work, amino acids were given throughout the day for each of the first three days. This was changed later to a program in which up to 1,500 cc. of the 8 per cent amino acid solution were given both morning and evening by infusion, supplemented by a clysis of 1,500 cc. of 5 per cent dextrose in saline, in the morning. The patients received water by mouth for the first two to three days after operation. A standard postoperative gastric feeding regimen was then started. Food intake was increased as rapidly as tolerated. As the calories increased by mouth, the dextrose in saline was omitted. As the protein intake became greater, the amount of the amino acid infusion was reduced. Thus, most patients received amino acids in decreasing quantities for about six days after operation. Determinations of venous pressure and vital capacity[12] were made when there was doubt as to cardiac function. Blood urea nitrogen, carbon dioxide content, chlorides, hematocrit, red blood cell count, and plasma proteins were determined by standard methods,[13-17] the blood chemistry estimations being done two or three times a week postoperatively.

RESULTS

Healthy Subjects: A preliminary short-term experiment was conducted to confirm the adequacy of the VUJ mixture of pure amino acids as a substitute for protein in the diet. Two young healthy men, working as orderlies in the hospital, were placed on a weighed diet with 90 Gm. of protein per day and 3,000 calories. When nitrogen equilibrium was established for a week, 1,000 cc. of 8 per cent amino acid solution by infusion were substituted for 60 of the 90 Gm. of protein in the diet. Some food protein was given in order not to alter the ratio of protein, fat and carbohydrate on which nitrogen equilibrium had been produced. The substitution of amino acid for the food protein produced no significant change in nitrogen balance during the two days of its use or in the next few days.

Preoperative Patients: The mixture of pure amino acids was given to 15 patients before operation. In six of the patients, the amino acid solution was

† Dr. Warren Cox and Mr. A. Hill, of the Mead Johnson Co., kindly supplied the casein hydrolysate (Amigen) for oral and parenteral use.

TABLE II

SHOWING PREOPERATIVE NITROGEN BALANCE WITH A MIXTURE OF PURE AMINO ACID AS A SUPPLEMENT TO FOOD OR CASEIN HYDROLYSATE

Patient	Day Before Oper.	Food Nitrogen (Gm.)	Casein Hydrolysate Nitrogen (Gm.)	Amino Acid Nitrogen (Gm.)	Total Nitrogen Intake (Gm.)	Total N. Excretion Urine and Stool (Gm.)	Nitrogen Balance (Gm.)
J. B.	9	13.1			13.1	14.4	− 1.3
	8	15.8			15.8	13.7	+ 2.1
	7	15.8			15.8	14.6	+ 1.2
	6	16.6			16.6	10.7	+ 5.9
	5	18.0			18.0	12.9	+ 5.1
	4	17.0		9.5	26.5	19.4	+ 7.1
	3	16.9		9.6	26.5	18.5	+ 8.0
	2	18.6		9.6	28.2	13.4	+14.8
	1	10.4			10.4	19.8	− 9.4
G. McG.	4	1.1		26.9	28.0	24.1	+ 2.8
	3	0.9		28.9	29.8	26.8	+ 3.0
	2	0.4		28.8	29.2	28.7	+ 0.5
	1	0.3		12.3	12.6	14.0	− 1.4
S. K.	6			18.5	18.5	9.2	+ 9.3
	5		18.0	19.0	37.0	16.9	+20.1
	4		18.0	19.0	37.0	16.8	+20.2
	3		17.4	17.6	35.0	18.2	+16.8
	2		18.0	14.7	32.7	13.5	+18.2
	1			9.8	9.8	12.9	− 3.1
	0			12.2	12.2	15.9	− 3.7
M. F.	7	0.2	13.0	9.7	22.9	22.3	+ 0.6
	6	1.3			1.3	11.8	−10.5
	5	7.4	10.2	9.1	26.7	14.6	+12.1
	4	4.1	13.0	9.5	26.6	21.3	+ 5.3
	3	6.1			6.1	10.4	− 4.3
	2	10.6			10.6	6.8	+ 3.8
	1	11.1			11.1	5.8	+ 5.3
R. G.	14		19.8		19.8	22.0	− 2.2
	13		19.4		19.4	22.0	− 2.6
	12			14.0	14.0	15.8	− 1.8
	11			14.1	14.1	26.3	−12.2
	10			13.6	13.6	13.6	0.0
	9			9.7	9.7	20.6	−10.9
	8		13.2		13.2	16.2	− 3.0
	7		13.2		13.2	12.0	+ 1.2
	6				0.0	10.2	−10.2
	5		20.0		20.0	9.6	+10.4
	4		22.2		22.2	14.5	+ 7.7
	3	7.3			7.3	10.8	− 3.5
	2	29.4			29.4	9.9	+19.5
	1	30.5			30.5	15.5	+15.0
	0			14.0	14.0	12.8	+ 1.2
R. S.	7	0.1	19.2		19.3	10.2	+ 9.1
	6	0.8		13.9	14.7	3.3	+11.4
	5		6.6	14.3	20.9	17.9	+ 3.0
	4		12.8		12.8	26.9	−14.1
	3		12.8		12.8	14.9	− 2.1
	2			13.8	13.8	19.6	− 5.8
	1			13.4	13.4	16.9	− 3.5
	0			9.5	9.5	20.2	−10.7

given in addition to nitrogen taken in the diet or taken in a casein hydrolysate material (Table II). Nitrogen was retained when the nitrogen intake was high, whether the amino acids were given alone or as a supplement. However, smaller intakes of about 10 to 14 Gm. nitrogen, sufficient to maintain equilibrium when given as food, were not adequate when administered as pure amino acids, or as casein hydrolysate without food. Also, negative balance occurred and persisted for several days after changing from high to low nitrogen intakes. This is seen with changes in food nitrogen intake and is not peculiar to the parenterally given materials.

The small supplies of material in the early phase of the study limited efforts to study the adequacy of amino acid administration and glucose as the sole source of nutrition preoperatively, although this was accomplished postoperatively. More data are being accumulated.

Postoperative Patients: A total of 29 patients were given the mixture of pure amino acids as the only source of nitrogen for the first three to five days after operation. Calories were supplemented by glucose-saline solution. Twenty-one of the patients underwent partial gastrectomy for peptic ulcer, while the other patients had a variety of operative procedures. An additional six gastrectomy patients were followed as controls, in that they were treated exactly the same as the other gastric cases but were given no amino acids.

A. NITROGEN BALANCE AFTER PARTIAL GASTRECTOMY

The least amount of nitrogen lost by any of the six control patients subjected to partial gastrectomy and given no amino acids postoperatively, was 25 Gm. of nitrogen, in the first five days after the procedure. Seventeen of the 21 patients undergoing the same procedure (Table III; Charts 5 and 6) but treated with amino acids, lost varying amounts less than this (Table III; Charts 1–3). Three of these 17 patients remained in nitrogen balance for this period and six showed actual positive balance. There was considerable wastage of amino acid material, as shown by a high urinary nitrogen excretion. Some of the wastage may have been the result of the low calories supplied, so that part of the amino acids were diverted for fuel.

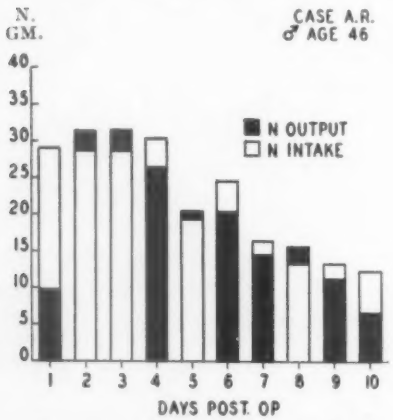

CHART 1.—Showing the production of nitrogen equilibrium after partial gastrectomy, by the use of a mixture of pure amino acids.

One peculiarity in the transition from amino acid to food intake was noted in three patients. When amino acid administration was stopped before an equivalent intake was achieved in the diet, the excretion of urinary nitrogen continued at a high level (Chart 4). This produced a consequent sharp negative balance which was sufficient, in a day or two, to exceed the total negative balance of the controls for the entire first five days after operation. This was prevented

TABLE III

SHOWING POSTOPERATIVE NITROGEN BALANCE FIGURES, AFTER PARTIAL GASTRECTOMY

N. Balance Gm. First 5 Days	Amino Acid Treated		
	Adequate	Inadequate	Controls
> +10	4	1*	0
0 +10	1	0	0
−1 −10	5	2	0
−11 −20	3	1	0
−21 −30	2	1	4
−31 −40	1	0	1
−41 −50	0	0	1

(* Renal damage.)

by reducing the amino acid in-put only as food intake was increased to the same degree.

(1) *Effect of Weight Loss Upon Nitrogen.*—Inanition and debility abolish the tendency toward negative nitrogen balance which usually occurs after injury. The weight loss of the patients was thus examined to determine if this was a factor in the retention of nitrogen. Seven treated cases with little or

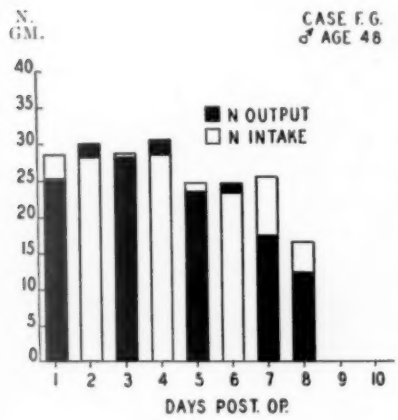

CHART 2

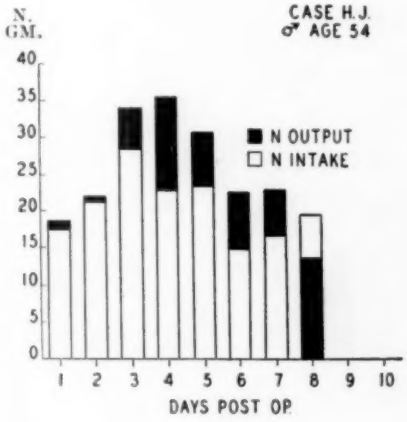

CHART 3

CHART 2.—Showing marked nitrogen sparing after partial gastrectomy, by the use of a mixture of pure amino acids.

CHART 3.—Showing the failure to spare nitrogen after partial gastrectomy with the use of a mixture of pure amino acids.

no nitrogen loss after operation and four treated cases with maximum nitrogen loss showed a difference (Table IV) in preceding weight loss. Two in each group had lost no weight but four had lost 25 to 30 pounds in the group retaining nitrogen, whereas, the greatest weight loss in the group not retaining nitrogen was 10–19 lbs. in two cases. Thus, although weight loss was not a reliable index of debility or of the ease with which nitrogen balance was going to be established, there was a tendency in the gastric cases to retain nitrogen more readily if the previous weight loss was marked.

(2) *Effect of Level of Amino Acid Administration.*—The data have been examined to determine if the level of nitrogen intake is important in the pro-

duction of nitrogen balance. A consideration of the amount of nitrogen administered to that retained indicates a relationship. Low nitrogen intakes of 0.11 to 0.30 Gm. N./Kg. body weight, were generally associated with negative balance and higher intakes with nitrogen sparing, if not balance. There is considerable variability. Unlike the situation before operation, no critical level of nitrogen intake was established beyond which nitrogen balance was uniformly produced, but no greater intake than 0.50 Gm. N./Kg. body weight was achieved.

TABLE IV

SHOWING RELATION OF WEIGHT LOSS BEFORE OPERATION TO NITROGEN BALANCE AFTER OPERATION, PARTIAL GASTRECTOMY TREATED WITH A MIXTURE OF PURE AMINO ACIDS

Preoper. Weight Loss % Average Body Weight	Nitrogen Balance					
	> + 10 (Gm. N.)	+10 to 0 (Gm. N.)	−1 to −10 (Gm. N.)	−11 to −20 (Gm. N.)	−21 to −30 (Gm. N.)	−31 to −40 (Gm. N.)
0	1	0	1	1	2	
1–10	1	0	3	2	1	1
11–20	3	1	2	1	0	0
21–30	0	0	1	0	0	0

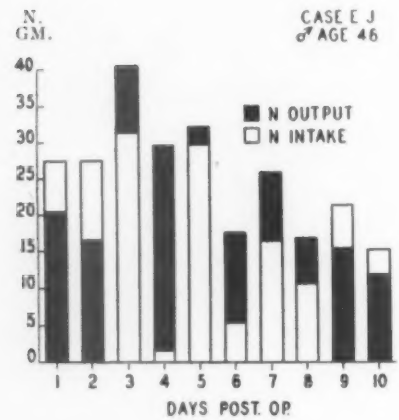

CHART 4

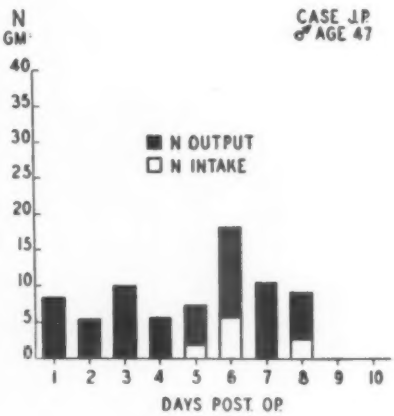

CHART 5

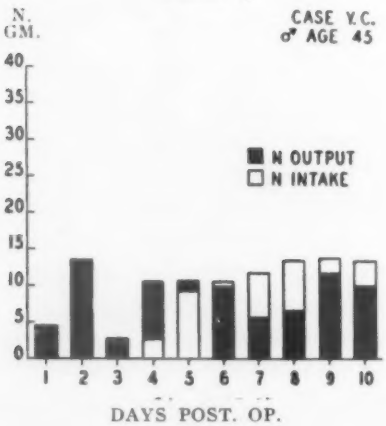

CHART 6

CHART 4.—Showing the continued outpouring of nitrogen after the sudden cessation of a high nitrogen intake, and the nitrogen sparing effect of resumption of high nitrogen administration.

CHARTS 5 and 6.—Showing nitrogen loss after partial gastrectomy on the usual postoperative regimen without amino acid administration.

(3) *Total Sulphate Excretion.*—The total sulphate excretion in the urine was determined to see whether retained nitrogen was used for protein synthesis. Sulphate excretion tended to parallel nitrogen output (Chart 7). The sulphur-nitrogen ratio averaged about 1 : 15. Thus, the variations in nitrogen balance probably involved tissue protein sources.

B. NITROGEN BALANCE IN CASES OTHER THAN GASTRECTOMY

Eight operative patients, other than the gastrectomy cases, were given as high nitrogen regimens, as possible by parenteral route, immediately after operation and the effect of nitrogen balance observed. This group had, in general, been healthy prior to operation and had lost no weight, except the two pancreaticoduodenectomy patients. All received the VUJ mixture of pure amino acids until the food intake provided about 15 Gm. of nitrogen per day. A casein hydrolysate was occasionally used to supplement the amino acid mixture when the supply of the latter had run out. In addition, two fracture patients were studied, a man and a woman in good health prior to the accident. The fractures were severe,

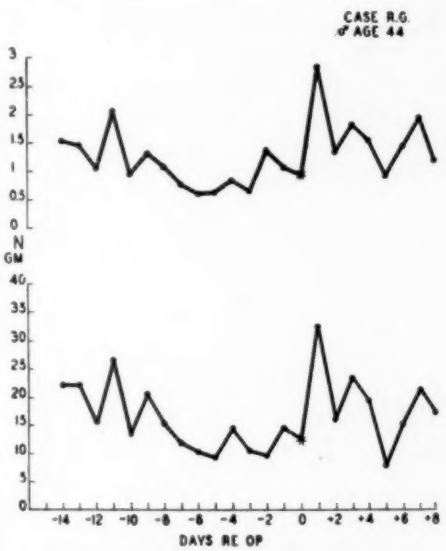

CHART 7.—Showing the parallel excretion of total nitrogen and total sulphur before and after partial gastrectomy and amino acid administration.

TABLE V

SHOWING EFFECT OF TREATMENT WITH A MIXTURE OF PURE AMINO ACIDS UPON NITROGEN BALANCE AFTER MISCELLANEOUS OPERATIONS UPON PREVIOUSLY HEALTHY PATIENTS

		Treated Cases				Untreated Cases		
Diagnosis	Patient	Days of Rx	Total Intake (Gm. N.)	Total Output (Gm. N.)	Daily Balance (Gm. N.)	Days	Daily Balance (Gm. N.)	Source
Acute appendicitis with appendicectomy.....	D. C.	5	120.7	120.8	−0.0	4	− 3.3	Grossman *et al.*[35]
	L. J.	3	64.9	69.5	−1.5	7	− 3.6	
	J. C.	3	76.0	95.7	−6.6	3	−10.3	
	C. M.	4	95.6	107.4	−3.9	7	− 3.3	
Hernia repair.....	C. Q.	4	71.4	75.2	−0.9	5	− 0.2	Grossman *et al.*[35]
	A. E.	4	89.0	80.1	+2.1	6	− 3.3	
Pancreatoduodenectomy.....	L. C.	5	94.7	123.4	−5.7	10	− 2.4	Brunschwig *et al.*[37]
	A. K.	5	90.2	108.4	−3.6	10	− 6.1	
Perforated ulcer.....	E. McK.	5	85.9	131.4	−9.1	10	−13.6	Brunschwig *et al.*[37]
Fracture.....	B. McN.	22	835.5	788.4	+2.1	39	− 4.9	Howard *et al.*[23]

one of the lower third of the femur with much soft-part damage, treated by a plaster encasement after closed reduction, and the other both bones of the leg with open reduction. The man was placed on a diet of 60 cc. of a 30 per cent solution of casein hydrolysate and 100 to 120 cc. of high protein milk every hour for eight to 12 hours, and the woman on a fixed diet with 90 Gm. protein and 2,500 calories supplemented with casein hydrolysate.

Nitrogen loss was decreased in half of the operative patients of this group, as compared to control figures in the literature for nitrogen loss after corresponding procedures (Table V). A discussion of the failures follows later in the paper. The fracture patients were maintained in nitrogen equilibrium after the trauma (Table VI), as opposed to the experience of Cuthbertson and

TABLE VI

TABLE SHOWING THE MAINTENANCE OF NITROGEN BALANCE IN A PREVIOUSLY HEALTHY MAN AFTER FRACTURE OF THE LOWER FEMUR WITH CONSIDERABLE SOFT-PART DAMAGE (TREATMENT WITH PLASTER ENCASEMENT), THE EARLY FAILURE OF PLASMA PROTEIN AND HEMATOCRIT TO BE MAINTAINED IS ILLUSTRATED

Case: B. McN. Male. Age 66.

	N. Intake (Gm.)			N. Output (Gm.)						
Day Post Injury	Food	Casein Hydrolysate	Total	Urine	Stool	Vomitus	Total	Nitrogen Balance (Gm.)	Plasma Protein (Gm. %)	Hematocrit (%)
3	8.5	14.7	23.2	32.5			32.5	− 9.3		
4	12.5	21.9	34.4	27.4	0.4	0.3	28.1	+ 7.0	6.4	36.9
5	14.5	23.1	37.6	34.3	0.4		34.7	+ 2.9		
6	14.9	23.2	38.1	21.5	1.7		23.2	+14.9	5.5	29.8
7	14.5	21.2	35.7	26.8	2.1		28.9	+ 6.9		
8	20.2	23.3	43.5	41.9	2.1		46.1	− 0.5		
9	18.8	23.2	42.0	36.0	0.9		36.9	+ 5.1	6.3	33.0
10	23.8	26.9	50.7	41.3	0.9		42.2	+ 8.5	6.5	34.8
11	23.9	28.7	52.6	40.7	1.7		42.4	+10.2	7.0	38.0
12	23.9	29.2	53.1	49.8	1.7		51.5	+ 1.6	6.9	37.0
13	22.0	29.5	51.5	49.0	5.4		54.4	− 2.9	6.8	35.5
14	23.8	28.6	52.4	46.6	1.8		48.4	+ 4.0	6.5	35.8
15	23.9	29.3	50.2	45.9	1.8		47.7	+ 2.5		
16	20.2	23.2	43.4	47.4	1.7	0.1	49.2	− 5.8	6.8	37.2
17	19.7	23.4	43.1	39.9	3.7	0.8	44.4	− 1.3	6.1	38.1
18	19.5	23.4	42.9	43.1	2.8		45.9	− 3.0	7.5	42.3
19	15.8	11.2	27.0	24.5	1.9		26.4	+ 0.6	6.9	42.2
20	18.5	11.9	30.4	30.2	1.9		32.1	− 1.7	7.3	43.7
21	15.9		15.9	21.5	1.8		23.3	− 7.4	7.4	43.7
22	18.0		18.0	16.3	1.9		18.2	− 0.2		
23	18.3		18.3	14.8	1.8		16.6	+ 1.7		
24	15.7		15.7	15.4	1.8		17.2	− 1.5		

of Howard. A discrepancy was noted between nitrogen balance, plasma protein and red cell count in that the latter values fell during the first two weeks after the fracture despite the maintenance of nitrogen balance.

DISCUSSION AND CONCLUSIONS

The healthy adult remains in nitrogen equilibrium except for minor daily fluctuations. Slight changes in nitrogen intake result in a corresponding retention or loss of nitrogen from tissue reserves.[18, 19] This implies a balance between nitrogen synthesis and breakdown provided the minimal glucose and caloric

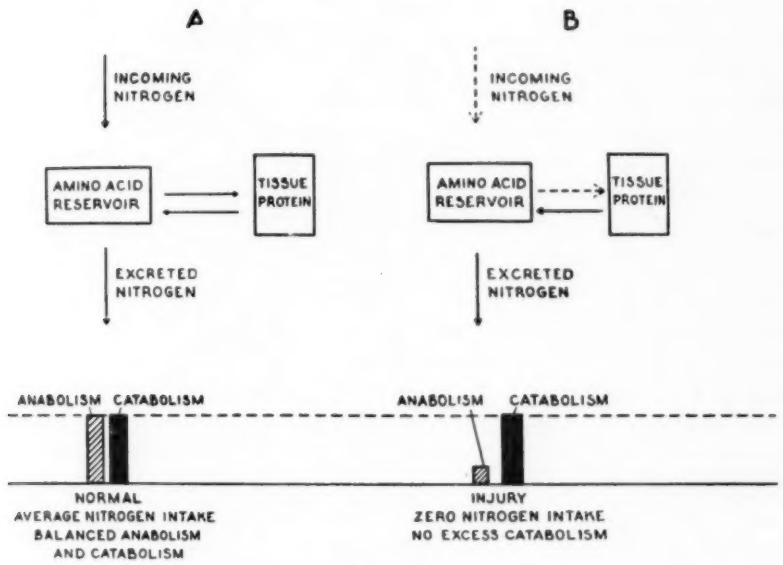

CHART 8

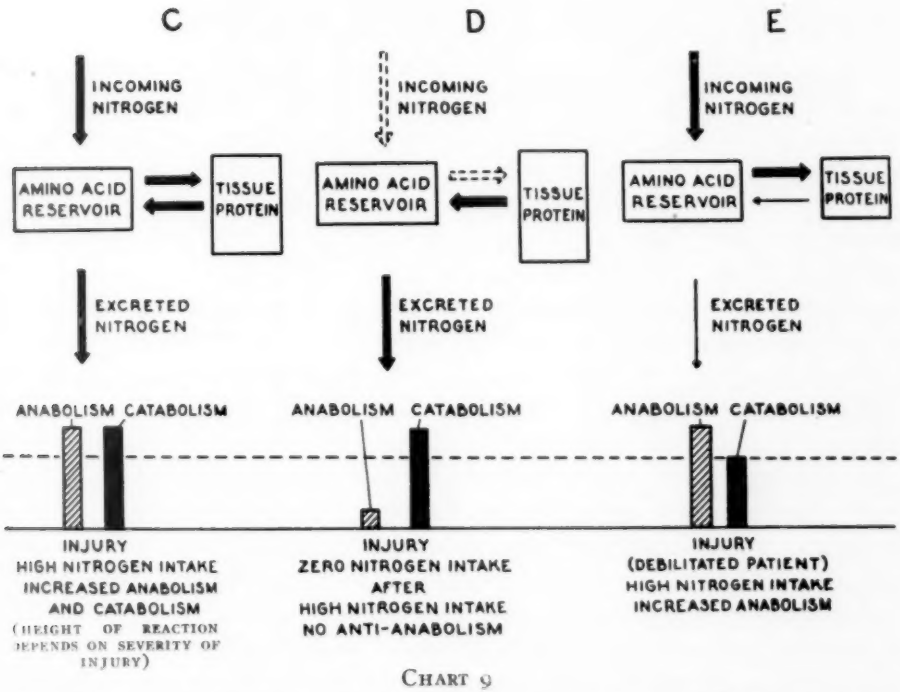

CHART 9

CHARTS 8 and 9.—Presenting a schematic representation of the changes in nitrogen balance which occur after injury. (Form of diagram suggested by Albright.[31])

requirements have been met (Chart 8a). Incidentally, this equilibrium point is somewhat higher in the men in this series,[20] 15 Gm. of nitrogen intake per day (95 Gm. protein) than the commonly accepted one of 10 Gm. (60 Gm. protein).

After injury, there is an acute change and a negative balance occurs when the nitrogen intake is maintained at previous levels. This loss of nitrogen has been called the toxic destruction of protein and has been discussed since before 1894.[3] Cuthbertson[21, 22] revived the concept that injury was followed by a phase of catabolism, since he could not restore his patients to nitrogen balance even with moderate increases in nitrogen intake. He has been supported in this view by Howard, and others.[23, 24] However, a catabolic response implies that stopping nitrogen intake from the time of injury would, if anything, increase the loss of nitrogen from the body. The data of the present study show that this is not the case (Chart 8b). No excesses of nitrogen appear in the urine when nitrogen is withheld postoperatively and, in fact, the nitrogen excretion may be less than that of an uninjured patient on the same intake. Also, high carbohydrate regimens spare nitrogen[1] which is unlikely if the nitrogen loss is the result of a true toxic destruction of tissues. Thus, there is no increased rate of catabolism or tissue destruction in the absence of nitrogen intake, and the "catabolic phase" of injury is not an accurate description.

A different theory to explain the inability to spare nitrogen has been advanced, namely, that incoming nitrogen is routed through the liver after trauma and is wasted before it can be used for anabolism by the tissues. Thus, the loss of nitrogen is "antianabolic" rather than "catabolic."[25] However, the data of the present study indicate that incoming nitrogen is not entirely wasted, so that a high nitrogen intake lessens or reverses negative nitrogen balance after trauma (Chart 9c). This is evident when the nitrogen lost by the treated patients is compared with that of the untreated controls in the gastrectomy group, or with the figures in the literature for loss after the other procedures and especially fracture. CoTui, *et al.*,[26] Brunschwig, *et al.*,[27] Levenson, *et al.*,[28] and others, have presented data similar to those of the present study. Thus, it is clear that the mechanisms for nitrogen retention or anabolism remain operative after injury so that an "antianabolic" explanation of events is dubious. Further evidence against a solely antianabolic effect is seen when a high nitrogen intake after operation is suddenly stopped. Nitrogen continues to be poured into the urine and must come from the tissues (Chart 9d).

Thus, the behavior of the nitrogen balance after injury is not satisfactorily explained by either the catabolic or antianabolic theories. The simple assumption that there is an increase in the rate of both anabolism and catabolism, rather than a change in either, appears to solve the discrepancies. It explains the fact that an increased nitrogen intake can reëstablish nitrogen equilibrium and that more or less than this amount results in varying degrees of positive or negative nitrogen balance as in the healthy subject. It also explains the continued outpouring of nitrogen from the tissues when the high nitrogen

intake is suddenly stopped. The fact that this evidence of increased catabolism is not present if nitrogen has not been given after the trauma, indicates one necessary condition in addition to the injury, for the response to be elicited, namely, the presence of incoming nitrogen. Another condition is that there have not been recent preceding injuries or body wasting from inanition. Madden[29] has suggested that reserve protein stores[18] are necessary for the reaction to trauma to occur. It is also possible that the mechanisms for catabolism, under these conditions, become too inactive to be easily activated by a new insult, so that nitrogen sparing continues to predominate (Chart 9e). A third factor is the severity of the injury, in that the more severe the insult, the more nitrogen is needed to restore equilibrium, *e.g.,* fractures versus partial gastrectomy.

In this connection, the use of gastric patients to study postoperative nitrogen balance lends itself to the just criticism of Peters[30] that such patients may be debilitated and may not be able to respond with a vigorous trend towards negative balance. Such a tendency is shown by the gastric cases of this series. However, three gastric cases put into nitrogen equilibrium had lost insignificant amounts of weight, and so were presumably otherwise healthy as were the fracture cases and the miscellaneous cases which were spared nitrogen. Also, the variations in amounts of nitrogen retained in the gastric cases after a given intake of nitrogen suggests that the usual reaction to trauma is operative. It is, therefore, felt that the nitrogen sparing from therapy is not entirely the result of debilitation and that the results are in line with those of Brunschwig, and the other workers, previously mentioned.

The significance of the fact that some patients were not restored to nitrogen balance, or spared nitrogen, deserves discussion. It is possible that these cases represent instances of a pure catabolic or antianabolic response to trauma. It is equally possible that insufficient nitrogen was given. With the pure amino acid mixture, the volume of fluid required and tendency to acidosis makes it practically impossible to administer more than 28 Gm. of nitrogen a day. Thus, the nitrogen needs after a particularly vigorous reaction to trauma, such as with the two fracture cases, could not be met by parenteral feeding, and a negative nitrogen balance would occur. It is generally agreed that the intensity of the reaction to injury depends on the severity of the injury and the reactivity of the patient. Thus, it is felt that the cases with negative nitrogen balance, despite amino acid administration, represent a particularly vigorous response to injury wherein the nitrogen needs exceeded the amount of nitrogen administered. This is the reason for the failure of most investigators to overcome the tendency to negative nitrogen balance—not enough nitrogen was given.

It should be mentioned that the attainment of nitrogen balance does not mean that individual protein functions may not still be disturbed. Although the parallel retention of sulphur and nitrogen suggests that protein is being formed when nitrogen loss is diminished, as shown by the fracture patient, plasma protein and hematocrit may fall notwithstanding this. Thus, some tissues apparently build protein while others do not, and such a derangement may not be

reflected by the over-all nitrogen balance. The change is possibly too great to be explained by the factor of hemodilution.

Finally, it is of interest to determine whether the effects of nitrogen administration upon nitrogen balance are reflected on the clinical course of the patients. This is discussed in the next paper (PART III) of this series.

SUMMARY

1. A study has been made of the effect of a mixture of pure amino acids on nitrogen balance as a supplement to food or a casein hydrolysate preoperatively, and as the sole source of nitrogen for the first 3–5 days postoperatively.

2. Nitrogen was spared in varying amounts in the majority of 21 gastric cases undergoing partial gastrectomy as compared to the nitrogen loss of six untreated controls. Eight other patients with miscellaneous conditions were studied and nitrogen sparing was produced in four.

3. Two previously healthy patients with severe fractures of the femur were maintained in nitrogen balance with a casein hydrolysate and high protein milk by mouth.

4. The nature of the reaction to injury is discussed and a simple hypothesis presented.

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PART III

CLINICAL RESULTS

IN THE PRECEDING PAPERS[1, 2] the suitability for clinical use of a mixture of pure amino acids has been established[1] and its effect upon postoperative nitrogen balance has been discussed.[2] Moreover, it has been postulated that the nature of the reaction of the body to injury, as far as nitrogen balance is concerned, is not solely upon anabolism, *i. e.*, antianabolism, or catabolism, but represents an increased stimulus to both, so that nitrogen equilibrium can be attained only at an increased level of nitrogen exchange. The present paper presents the clinical results from the high nitrogen intakes provided after operation by the use of the mixture of pure amino acids. Controlled observations of this sort are needed, since opinions vary considerably as to the value of high protein regimens after injury,[3, 4] and since few adequate reports of this nature are available.[5]

A type of surgical patient was selected for the present study, whose behavior after operation has been closely followed for many years, namely, ulcer patients subjected to partial gastrectomy.* All of these were treated in a similar manner pre- and postoperatively, except that the pure amino acid mixture was given to half the patients. The procedures and methods are outlined in the preceding paper. The observations were carried out over the past one and one-half years.

RESULTS

Twenty cases of peptic ulcer and one case of lymphoma of the stomach, without visible mestastasis, were submitted to partial gastric resection and given the pure amino acid mixture during the immediate postoperative period. All were males. During this same period 29 cases of ulcer were similarly operated upon on the same division (L-floor) but were not given amino acid therapy. Nineteen of these were males. Age distribution, race, weight loss before operation, and the incidence of early ambulation were similar in the treated and control groups. These figures are presented in Tables VII, VIII, IX and X. The charts of 26 additional cases of partial gastrectomy for ulcer operated upon on another surgical division (K-floor) and in the Private Pavilion during the period of this study, are tabulated, for interest, as controls. They received no amino acids postoperatively but their treatment was not as uniform as in the control cases on the same surgical service as the amino acid-treated cases.

The choice of objective criteria by which to evaluate the results of amino acid therapy is greatly limited. The day on which the patient leaves the hospital,[5] the day after operation on which the temperature returns to normal, and the ability to progress with a postoperative diet provide data which can be compared with that of the controls and may be reasonably related to nitrogen intake. Also, a phenomenon of stasis and poorly functioning gastro-

* Dr. F. B. St. John kindly granted permission to study the cases on his Service.

TABLE VII

SHOWING AGE INCIDENCE

Age	Amino Acid-Treated	L-Controls	K-Controls	Private Controls
< 31	1	1	2	0
31 to 40	3	9	5	3
41 to 50	12*	11	3	7
51 to 60	3	5	5	
> 60	2	1	1	

* One case of lymphoma.

TABLE VIII

SEX INCIDENCE IN RELATION TO DAY OF DISCHARGE FROM THE HOSPITAL AFTER PARTIAL GASTRECTOMY

Day Home Postoperative	Amino Acid-treated	L-Controls		K-Controls		Private Controls	
	Male	Male	Female	Male	Female	Male	Female
21 or before	19	17	4	8	4	6	2
22 or after	0	5	1	2	1	2	0
Died	2	0	1	1	0	0	0
Total	21	22	6	11	5	8	2

TABLE IX

YEAR OF OPERATION IN RELATION TO DAY OF DISCHARGE FROM HOSPITAL AFTER PARTIAL GASTRECTOMY

Day Home Postoperative	Amino Acid-treated		L-Controls		K-Controls		Private Controls	
	July-Dec. 1944	Jan.-Sept. 1945	July-Dec. 1944	Jan.-Sept. 1945	July-Dec. 1944	Jan.-Sept. 1945	July-Dec. 1944	Jan.-Sept 1945
21 or before	5	14	7	14	5	7	4	4
22 or after	0	0	3	3	2	1	0	2
Died	1	1	0	1	1	0	0	0
Total	6	15	10	18	8	8	4	6

enterostomy in postoperative gastrectomy cases occurring a week after the procedure may be observed since this complication may be nutritional in origin.[6] Clinical impressions of strength and well-being are apt to lead to erroneous conclusions and only a statement about these is warranted, as a rule.

Day of Discharge: Table XI indicates the day of discharge after operation and indicates that 11 of the 54 control patients not receiving amino acids remained in the hospital 21 days or more. The complications causing this delay are listed in Table XII. Most of these may reasonably be related to inadequate nitrogen nutrition. None of the 19 surviving cases treated with the amino acid mixture were kept beyond the 21st day. In the untreated series, there were two deaths. One was directly attributable to complications from operation, which may have stemmed from poor nutrition. The other died of gas gangrene of the abdominal wall one day after operation, and, so, death was probably not precipitated by any nutritional factor. In the treated series, there were also two deaths. One resulted from peritonitis from an undiagnosed volvulus of the intestine, after four days of apparently good progress. The other was also not attributable to protein depletion but may have died as the direct result of the amino acid administration. This case is discussed in detail in the first paper of this series.

TABLE X

NUMBER OF CASES ALLOWED EARLY AMBULATION IN RELATION TO DAY OF DISCHARGE FROM HOSPITAL AFTER PARTIAL GASTRECTOMY

Day Home Postoperative	Amino Acid-treated		L-Controls		K-Controls		Private Controls	
	Amb.	Not Amb.	Amb.	Not Amb.	Amb.	Not Amb.	Amb.	Not Amb.
21 or before	15	4	13	8	9	3*	6	2
22 or after	0	0	4	2	2	1†	2	0
Died	1	1	0	1	0	1	0	0
Total	16	5	17	11	11	5	8	2

* One allowed up on day 6. † Allowed up on day 6.

TABLE XI

DAY OF DISCHARGE AFTER PARTIAL GASTRECTOMY

Day Home Postoperative	Amino Acid-treated		L-Controls	K-Controls	Private Controls
	Adequate Rx	Inadequate Rx			
14 or before	8	3	8	4	2
17 to 15	2	1	8	6	6
21 to 18	5		5	2	
25 to 22			2	1	
30 to 26			1	2	1
40 to 31			3		1
Died	1*	1†	1	1	
Total	16	5	28	16	10

* Volvulus. † Acidosis?

TABLE XII

TABLE SHOWING POSTOPERATIVE COMPLICATIONS IN PATIENTS NOT TREATED WITH AMINO ACID MIXTURE, LEAVING HOSPITAL 21 DAYS, OR MORE, AFTER PARTIAL GASTRECTOMY

Name	Floor	Age	Wt. Loss before Oper. (6 mos. or less)	Day Home	Postoperative Complications
I.K.	L	49	0	Died	Subphrenic abscess day 4, with drainage. Hemorrhage day 18. Jejunostomy day 25, to try to feed and raise plasma protein level of 4.46%. Died day 25.
J.W.	K	72	30	Died	Gas gangrene abdominal wall and died day 1.
T.M.	L	39	10	51	Distention marked to day 7. Perforated duodenal stump day 15, with exploratory operation. Inability to void and cystitis throughout.
A.M.	L	60	33	38	Pneumonia day 3. Parotitis day 7. Edema stoma and poor emptying (x-ray) day 25. Wound ooze until discharge.
M.S.	P.P.	45	10	34	Pulmonary infarct day 7. Vomiting and gastric residue day 21.
J.D.	L	46	0	30	Repair perforated ulcer 37 days before partial gastrectomy. Resection of ulcer 10 days before partial gastrectomy. Pneumonitis day 3 and continued fever to day 14 after partial gastrectomy.
N.S.	P.	50	0	27	Soft distention to day 5. Vomiting with x-ray evidence of poorly emptying stoma, day 12.
A.L.	L	37	0	27	Pneumonitis day 4. Pulmonary infarct day 9. Renal pain left, day 19.
H.S.	K	56	0	26	Continued fever to day 15, with tender mass in RUQ spontaneously subsiding. Cystic necrosis of omentum.
M.M.	K	48	0	25	Continued fever to day 18 and pancreatic fistula day 6 on.
L.McD.	L	43	0	24	Gastric retention, with x-ray evidence of edema of stoma and poor emptying day 11.
J.W.	L	48	0	23	Jaundice day 5. Cephalin flocculation negative. Alkaline phosphatase 7.9 B.U. plasma protein 5.3%.
W.C.	L	39	10	22	Plasma protein 4.9%. Gastric residue and vomiting to day 18.

TABLE XIII

SUMMARY TABLE SHOWING THE DAY OF DISCHARGE FROM HOSPITAL AFTER PARTIAL GASTRECTOMY

Day Home Postoper.	Amino Acid-treated Cases	L-Controls	K-Controls	Private Controls
Day 21 or before	19	21	12	8
Day 22 or after	0	6	3	2
Died	2*	1	1	0
% > 21 days	0	19.2	20.0	20.0

* Volvulus, and acidosis

Return of Temperature to Normal: The temperature after partial gastrectomy generally returns to normal by the 4th or 5th day after the procedure. In six of the 29 untreated cases, the fever did not subside until the 11th to 30th day. None of the amino acid-treated patients maintained a rise in temperature beyond the 11th day. This data is tabulated in Table XIV.

TABLE XIV

POSTOPERATIVE DAY WHEN TEMPERATURE RETURNED TO NORMAL AFTER PARTIAL GASTRECTOMY

Postoperative Day	Amino Acid-treated	L-Controls	K-Controls	Private Controls
1		1		
2	2			
3	11	1	3	
4	5	6	1	5
5	1	7	1	
8 to 6	0	4	3	
11 to 9	2	2	0	1
20 to 12	0	4	3	
> 20			1	
Died	2	1		

TABLE XV

POSTOPERATIVE DAY AT WHICH PATIENT COULD EAT A BLAND DIET AFTER PARTIAL GASTRECTOMY

Postoper. Day	Amino Acid-treated	L-Controls	K-Controls	Private Controls
10 or <	4	2	5	3
15 to 11	13	18	7	5
20 to 16	2	2	2	
25 to 21		3		
Died	2	1	1	

Abdominal Distention and Postoperative Edema of the Gastro-enterostomy Stoma: The incidence of these complications in the controls was definite, though perhaps too low to make comparisons significant. There were five cases of distention and five cases of late vomiting with gastric residue, in this group. Three of the latter five had roentgenograms to confirm the slow emptying and edema of the stoma. None of the treated cases showed these symptoms.

Ability to Progress with a Postoperative Diet: Appetite and ability to eat a bland diet may have been improved by the amino acid therapy (Table XV). No instance of postoperative anorexia was noted in the treated series and all cases were able to add to their diet progressively. An ambulatory ulcer regimen, with 100+ Gm. protein, was eaten, without objection, by day 12 after operation. The controls appear to have added foods to the diet almost as well as the treated cases, but the amount of food consumed was occasionally less than that provided by the diet. Figures relevant to intake are available in only 16 control cases, but show that five of the 16 were unable to keep up with their diet. It was noted that both the treated patients and the untreated controls with good appetite can progress much faster in respect to caloric and protein intake than the usual postoperative regimens permit.

Well-being and Strength: The impression was gained that the treated patients were stronger than some of the controls, at the time of discharge. This point was not tested objectively.[7]

DISCUSSION AND CONCLUSIONS

There are three possible objections to forming final conclusions from the present study about the benefits to be derived from amino acid therapy after operation. First, the series is small. However, the cases are unusually uniform in respect to procedure, treatment, preceding weight loss, age, and the use of early ambulation.[8] Thus, minor differences may have more significance than in a larger but less homogeneous group. Also, the series is bigger than most of those from which conclusions have hitherto been drawn.[5, 9, 10] Second, only one-fifth of the control cases appear not to do as well as the treated ones. However, most of these patients are not severely protein depleted before operation so that, again, a slight change in recovery rate may be more significant than a similar small percentage in a more debilitated group. Third, the criteria used may not necessarily reflect protein depletion and repletion. The fact that both groups were identical except for the use of amino acids suggests that if there is any real difference in the behavior of the two groups, it must be the result of this one variable.

Despite the difficulties of evaluation, a positive influence of the treatment with the pure amino acid mixture is suggested by the data. Eleven of the controls stayed in the hospital considerably longer than any of the treated cases, and failed to restore their temperature to normal as quickly or to eat as well. Furthermore, five of these developed objective difficulties at the gastroenterostomy stoma, with gastric retention and roentgenographic changes, in the 2nd week after operation, whereas, none of the amino acid-treated cases showed this. Thus, a trial of this material in a larger number of patients appears warranted, to see if these results can be confirmed. Only uniformly treated and controlled groups of cases should be used, however, if useful data is to be obtained. Otherwise, the results cannot be interpreted. In any event, the results are not sufficiently distinct from those of the controls to indicate that routine unconsidered protein hydrolysate or amino acid therapy is necessarily of benefit.

Obviously, not all surgical patients will need a high nitrogen intake. The healthy individual has more than enough protein reserve to handle any acute injury. But where the drain on rotein stores threatens to be protracted, as after fracture, or has been severe as with burns, repeated trauma or infection, such therapy seems indicated to conserve nitrogen and to avoid the complications of protein depletion,[11-14] if possible.

The question then arises as to whether the best procedure is to force nitrogen intake before or after operation, or at both times. Positive nitrogen balance is produced readily before injury, but with difficulty afterwards, so that there is no doubt that the preoperative period should be used to full advantage. However, definite amounts of nitrogen can be spared to the body after injury in many patients. Thus, if body nitrogen stores have been depleted by weight loss, gastric retention, anorexia, hemorrhage, secondary operation or infections[15] before or after operation or injury, a high nitrogen regimen is indicated after the procedure, as well as before.

If such a regimen is desired either before or after operation, the ability to eat and retain food becomes important. A practicable parenteral regimen has been outlined[2] which meets body nitrogen requirements by the use of mixture of pure amino acids and glucose-saline solution, when the patient cannot take nourishment by mouth. Nausea, acidosis, low calories and the large volumes of fluid required are the difficulties encountered, although sodium lactate (⅙ molar) solution and a rate of administration of 400 cc. per hour of the 8 per cent amino acid solution generally prevent the first two of these complications. The wastage of nitrogen by this method is high, so that 20-28 Gm. of nitrogen may be needed to insure nitrogen sparing for most patients. But nitrogen is spared, especially in the debilitated patient in whom significant nitrogen loss is undesirable.

However, when some food can be eaten, the amino acids find their most efficient use, namely, to supplement an inadequate intake to achieve a normal or high nitrogen level. The equivalent of 60 Gm. of protein can be given in a liter of fluid, in a 2.5-hour period, and most of this nitrogen is retained.[2] Incidentally, the infusions produce anorexia for several hours, so that the end of the day, after the patient has eaten, is chosen for the infusion, which is brief enough not to interfere with sleep.

Mention must be made of the work on high carbohydrate and high caloric intakes in sparing nitrogen after injury.[16] These regimens require very large intakes of food. If this can be achieved, with moderate nitrogen intake, there is no reason why this method should not be used. If the patient cannot eat the required amounts, the high nitrogen regimens discussed above are simpler and more practicable and will spare protein when needed.

SUMMARY

1. A clinical study has been made of the effect of postoperative treatment with a mixture of pure amino acids on the recovery from partial gastrectomy

The author is greatly indebted to Dr. Allen O. Whipple for his advice and continued interest in the entire project.

of 21 ulcer patients, as compared to 32 similar cases handled in the same way but not given the amino acid mixture.

2. A fifth of the controls appear to do less well than the amino acid-treated cases. However, the results in the two groups are similar enough to raise the suspicion that routine, unconsidered postoperative therapy with hydrolysates or amino acids may be in large part unnecessary.

3. The criteria of clinical benefit used are evaluated as are the indications for high nitrogen intakes before and after operation.

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THE CLINICAL BEHAVIOR OF ARTERIOSCLEROTIC ANEURYSM OF THE ABDOMINAL AORTA: A RATIONAL SURGICAL THERAPY

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IN A GROUP of 32 cases of aneurysm of the abdominal aorta admitted to the Presbyterian Hospital in recent years, arteriosclerosis was the cause of the aneurysm in 26. These aneurysms were fully developed, fusiform in shape and arose from the abdominal aorta three or more centimeters distal to the origin of the renal arteries. Syphilis was the etiologic agent in six of the 32 cases, these aneurysms being saccular and causing vertebral bone erosion in four instances. In this latter group the aneurysm arose distal to the renal arteries in only one of the six cases. There were only two females in the entire group of 32 cases, both having arteriosclerotic aneurysm, and the average age of those with arteriosclerotic aneurysm was 60 years while it was 42 years for the syphilitic group.

One gains the impression from the literature that there is a high incidence of vertebral erosion in aneurysm of the abdominal aorta but such was not the case in the arteriosclerotic group of our series. Of the 26 cases of arteriosclerotic aneurysm, vertebral erosion was noted in only one instance, and in this case, erosion was due to aneurysmal involvement of the right common iliac artery. Aside from the fact that the arteriosclerotic aneurysm is usually fusiform, it seems likely there may be another factor accounting in part for the rarity of bone erosion, namely, elongation of the abdominal aorta. Considerable elongation of the vessel seems an invariable precursor to the formation of the arteriosclerotic aneurysm of the abdominal aorta. In fact, a study of many specimens reveals, a few centimeters below the renal arteries, a sudden change in direction of the aorta, (usually forward, but often to the left or right), and immediately distal to this angulation the fusiform aneurysm begins. It is common at operation to note an angulation of the aorta sometimes as much as 90 degrees immediately proximal to the origin of the arteriosclerotic aneurysm, the latter scarcely touching the vertebrae. What may be the added effect upon angulation by flexion of the thoracolumbar spine is a matter of conjecture; and, of equal importance, the hemodynamic water hammer effect of strain upon the lower abdominal aorta consequent to angulation of the sclerotic iliac arteries by flexion of the thighs as in the sitting position. We speak of angulation of the arteriosclerotic artery in the sense of its walls buckling rather than bending with a gentle curve, as would a normal artery.

We know from experimenting with arteriosclerotic popliteal arteries that flexion angulation causes a water hammer effect of increased strain upon the popliteal artery lying immediately proximal, unsupported in the upper popliteal space. In our opinion, this is an important factor in the development of

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arteriosclerotic popliteal aneurysms and it seems likely that a similar mechanism may play a part in the development of the arteriosclerotic aneurysm of the lower abdominal aorta. As possibly having some bearing on the above discussion, it is of interest that, as far as our hospital service is concerned, the popliteal artery and the lower abdominal aorta are the common arteries affected by arteriosclerotic aneurysm. By this we mean well-developed aneurysms—not counting, of course, dissecting aneurysms of the sclerotic thoracic aorta.

As may be expected, the difference in pathology between the syphilitic and arteriosclerotic aneurysm of the abdominal aorta, as pertains to vertebral erosion, affects the incidence and severity of pain. Thus, the four syphilitic cases with vertebral erosion had for months received opiates for the control of severe radicular pain. Complete relief of pain following wiring and electrothermic coagulation of the aneurysm could only mean that the aneurysm became smaller in size following operation, thus, relieving pressure upon the spinal nerves. Unfortunately one of the four cases having a subluxation of the vertebrae died of infection following a bone graft procedure done some months after the wiring operation. The remaining three cases are alive, active and pain free now, eleven, seven and four years, respectively, following operation.

One gains the impression from the literature that the high incidence of vertebral erosion with resultant radicular (nerve pressure) pain is so constant in aneurysm of the abdominal aorta as to constitute a diagnostic sign. Our attention is called to the fact that vertebral erosion was present in only five of the 32 cases herein reviewed and in only one of the 26 cases in which the aneurysm was due to arteriosclerosis. This suggests, that in the past medical literature of the symptomatology of aneurysm of the abdominal aorta has been built up largely from syphilitic cases—cases which give a long drawn out history of severe pain due to nerve pressure from bone erosion.

Pain is the most important symptom that makes people seek medical relief. Due to the absence of bone erosion as an early cause of pain in the arteriosclerotic aneurysm of the abdominal aorta, the unfortunate victim of this disease often goes to the brink of disaster before seeking medical aid. A recent case illustrating this may be outlined as follows: A local physician called, stating that five days previously he had seen, for the first time, a 64-year-old man who gave a history of having, from time to time, for several months, a slight pain in the low back, including the sacro-iliac regions. The pain was exaggerated by bending forward or by exertion. Suddenly the pain became intense, radiating to the posterior aspect of the legs. Three days after onset the pain had extended up the back, over the abdomen, into the groins and down the anterior aspect of the thighs. On the fourth day of onset the patient began to vomit. When I saw the man, two days later (on the 6th day of his illness) he was under the influence of sedatives; pulse 84, B.P. 120/60. He appeared anemic but not in shock. The skin was warm and dry. The abdomen was not soft but neither was it distended with gas. A large, pulsating mass was present in the region of the abdominal aorta. The scrotal and perineal tissues were ecchymotic. An hematocrit made at this time was 23.8.

This man undoubtedly had had a large arteriosclerotic aneurysm of the abdominal aorta for months before having what he considered sufficient symptoms to warrant seeing a doctor. His first real nerve pressure pain comparable to the radicular pain of early bone erosion in the syphilitic case was actually caused by rupture of the aneurysm resulting in a spreading retroperitoneal hematoma.

Essentially, the story of pain from the beginning rupture of the aneurysm as the presenting symptom of consequence was elicited in 11 of the 26 cases of arteriosclerotic aneurysm. Some of the cases came under medical care with the history of less violent and more varied initial symptoms. Loss of weight is a common complaint in arteriosclerotic, as is the case with syphilitic aneurysm of the abdominal aorta. Eleven of the 26 cases of arteriosclerotic aneurysm had sustained weight losses varying from 15 to 35 pounds.

In five of the 26 cases of arteriosclerotic aneurysm a pulsating mass in the abdomen first directed attention to a diagnosis.

A sudden episode of severe, cramp-like abdominal pain, followed by collapse, was the apparent symptom of onset in a 51-year-old physician in whom, four months later, a well-developed fusiform arteriosclerotic aneurysm was palpable.

Severe hunger pains, combined with anorexia, punctuated the symptoms in another case—a man of 55, in which the aneurysm had been observed to grow to the size of a large grapefruit over a three and one-half-month period.

Our oldest case, a man of 72, had attacks lasting several days, which simulated ileus or duodenal obstruction. One of these attacks complicated our second-stage wiring operation. The old gentleman recovered, following Miller-Abbott intubation, however, and lived some two years, finally dying of a cerebral accident. Considering the great amount of forward displacement of the third portion of the duodenum, often seen in cases of large aneurysms, one marvels at the relative infrequency of symptoms of duodenal obstruction. Postoperative edema does add to this hazard, however, and in one other case we considered it a contributory cause of death. Again, contrary to what one would expect, in the relation of the transverse colon to a large aneurysm of the abdominal aorta, we have been surprised at the rarity of bad constipation.

We may close the discussion on the symptomatology of arteriosclerotic aneurysm of the abdominal aorta with a word of warning about pain. Analysis of the 26 cases of arteriosclerotic aneurysm affords convincing evidence that the appearance of deep-seated abdominal pain, low back pain and pain radiating to the hips or legs is a warning of impending disaster. Furthermore, my experience has been that the mortality of well-developed arteriosclerotic aneurysm of the abdominal aorta is quite as great as that of syphilitic aneurysm.

THE SURGICAL TREATMENT OF ANEURYSM OF THE ABDOMINAL AORTA

The ideal surgical therapy for degenerative arterial aneurysm entails cure of the aneurysm with maintenance of the arterial blood flow through the vessel affected. Whereas the above ideal has been successfully accomplished in

so-called peripheral aneurysm, in aneurysm of the aorta, where it has been considered essential to preserve arterial blood flow, we have been forced to rely upon blood clotting within the aneurysmal sac as our main bulwark against the continued growth of the lesion.

In the year 1935, with the valued aid of Professor Barry G. King, of the Department of Physiology of the College of Physicians and Surgeons, a series of investigations in the hemodynamics of aneurysm was begun. In the first place, when the yellow elastic tissue of the aorta wall is destroyed and the media gives way, the budding aneurysm is subjected to a strain which increases *pari passu* with its growth. Blood, circulating under pressure, creates a strain on the sac wall of an aneurysm varying with the square root of its surface area and, to a lesser extent, with the rate of blood flow. Doubling the diameter of the aneurysm, for example, increases the strain on the sac 100 per cent. The stretched sac is further devitalized due to failure of blood supply to the sac wall to keep pace with the expanding sac. Thus, there is a vicious circle in a growing aneurysm of increased strain upon a sac wall of diminishing strength.

On the other hand, clotting of an aneurysm does offer the advantage of the physical laws governing solids. To illustrate: when the fluid blood of a saccular aneurysm becomes a solid, the total strain upon the aneurysmal sac wall is reduced from the aggregate pressure exerted on the total surface area of the sac wall to that of the pressure exerted on the surface area of the mouth of the aneurysm only. The true magnitude of this reduction in strain is only fully appreciated when one stops to consider that the surface area of the mouth of the saccular aneurysm is usually but a small fraction of the total surface area of the sac wall. It is not surprising, then, in accordance with the above mentioned physical laws, that authentic instances of nature's cure of saccular arterial aneurysm have accumulated in the literature of pathology for over 100 years—cases in which clotting of the aneurysm had resulted in complete inactivation of the lesion—the patients having subsequently died of some other cause. It is but reasonable to assume that removing the strain upon the sac wall, caused by the expanding pulsations of fluid blood, by converting the blood to a solid blood clot affords the strengthening processes within the sac wall an opportunity to become effective.

Our studies revealed that the initiation and propagation of mass clotting within aneurysms is dependent largely upon two important factors: namely, (1) the presence of adequate stimulus to blood clotting; and (2) the rate of blood flow through the aneurysm. We have obtained rate of blood flow measurements in approximately 150 aneurysms. It is of extreme importance to note the great variations in the rate of blood flow. For example, in two saccular aneurysms of equal size the rate of blood flow through the aneurysm may vary as much as 300 per cent. The larger the mouth of a saccular aneurysm the higher the rate of blood flow through the aneurysm. In cases of so-called "cup-shaped" saccular aneurysms in which the diameter of the mouth of the sac is equal to, or exceeds, the diameter of the sac, the rate of blood flow

through the aneurysm is extremely rapid—approximating that of fusiform aneurysms.

One may correlate the relation of the rate of blood flow to spontaneous clotting within aneurysms by simply reviewing pathologic specimens. It is rare, indeed, to find any appreciable deposit of blood clot within fusiform or wide-mouth saccular aneurysms.

Thus, we see that nature's cure of aneurysm has been relegated usually to the occasional case of small-mouth saccular aneurysm in which conditions favor complete "brimful" clotting of the aneurysm.

The first attempts to induce clotting within aneurysm by the introduction of wire date back to Moore, in 1864. Fifteen years later, Corradi suggested the use of an insulated needle through which to pass silver wire into the aneurysm. The protruding end of bare wire was then connected to the positive pole of a battery, the negative electrode was applied to the skin in the neighborhood and a galvanic current passed. The resulting ionization product deposited at the surface of the wire was depended upon to encourage the initiation of blood clotting within the aneurysm. Subsequently, Colt advocated the introduction of multiple wisps of wire into aneurysms to act as a nidus for the initiation of blood clotting. A thorough review of published cases employing these wiring methods revealed a great uncertainty in the results with an occasional brilliant success. Now that we know of the great variation in the rate of blood flow in aneurysms and the relation of rate of blood flow to blood clotting, we can readily understand their results.

We now have conclusive experimental and clinical evidence that a method of wiring aneurysms to be efficient in the induction of mass (brimful) clotting must fulfill the following requirements: (1) it must afford an adequate and efficient clot-stimulating surface to the passing blood; and (2) it must furnish a means of measuring blood flow in the individual aneurysm as a guide to the amount of wire it is necessary to introduce to impede the blood to a rate of flow at which, in the presence of an adequate clot-stimulating surface, complete mass clotting of the aneurysm will take place.

METHOD

The electrothermic method of coagulating aneurysms embraces the use of fine (34-gauge B. & S.), insulated, coin silver wire sterilized by autoclave. The wire is introduced into the aneurysm in ten-meter segments through a special needle (Fig. 1). Five meters of wire are wound on each of two aluminum spools and bent into a loop in the middle for passage through the needle. This permits the two ends of the segment of wire to protrude from the needle for the purpose of establishing electrical contact.

A source of approximately 100 volts of direct current is used for the heating apparatus (Fig. 2). The current is so regulated (Fig. 3) and calibrated against changes in the electrical resistance of the wire upon heating as to show an accurate measurement of the temperature of the wire on a ratiometer at all times, and of the rate of blood flow through the aneurysm upon initial heating. Each ten-meter segment of wire is finally heated to 80° C. for

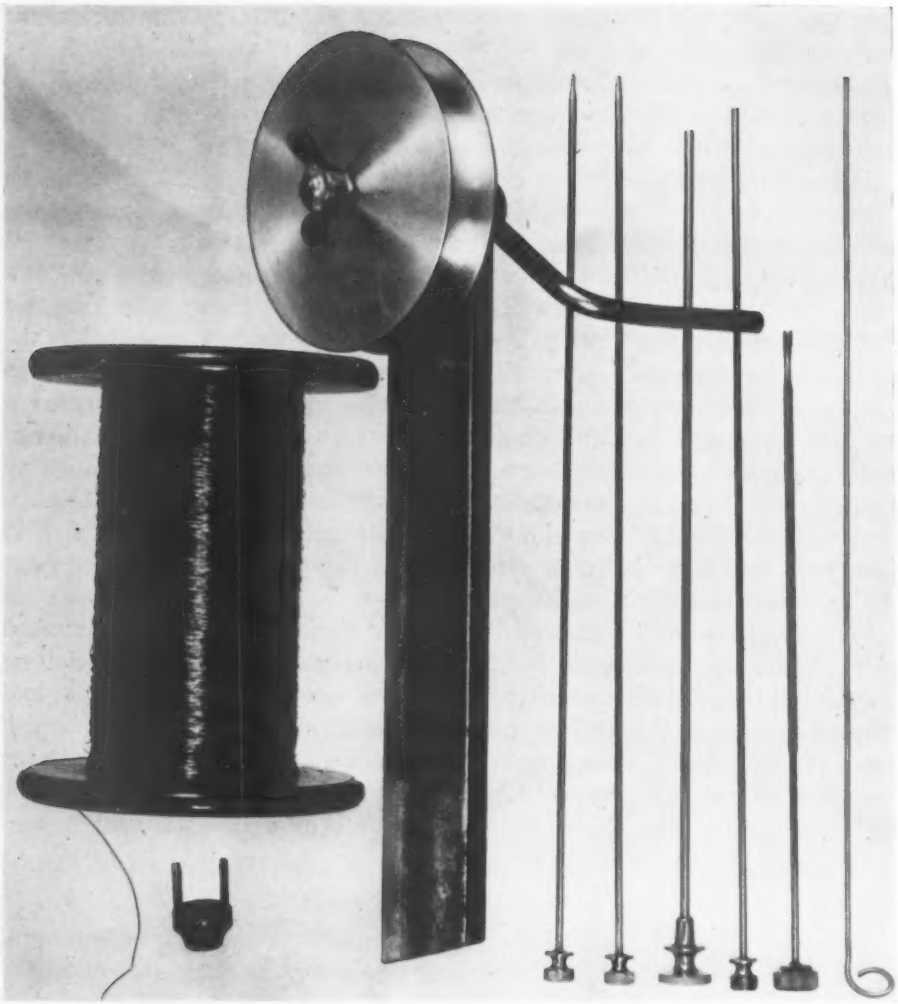

FIG. 1.—Armamentarium for Coagulating Aneurysm:

(A) Enameled wire on spool; (B) electrode cap, adapted to (G); (C) hand reel for winding wire on spools; (D) a trocar-pointed stylet adapted to (F) for traversing firm tissues and piercing the sac of the aneurysm; (E) tapered blunt stylet adapted to (F) for traversing tissue of lung; (F) 14-gauge, 6.5 in. needle made of stainless steel, with the end beveled from without in; (G) inner sheath for needle (F) which locks in place and has the end beveled from within out, fitting exactly with needle (F) to furnish a rounded nonabrasive end; (H) wire-passer adapted to (G), and (I) a blunt stylet adapted to (G).

a ten-second period. This results in the deposit of a tenacious, clot-stimulating, protein coagulum upon the wire.

On the basis of the number of amperes of current required to heat the first ten-meter segment of wire introduced into the aneurysm it is possible to determine the following: (1) the variety of aneurysm (based upon rate of blood flow); and (2) approximately the number of segments of wire it will be necessary to introduce into the aneurysm to impede the blood flow to the point of occurrence of mass clotting, namely, the requirement of three amperes to raise the temperature of a final segment of wire to 80° C.

To avoid the occurrence of "hot spots" upon heating and to promote a more even distribution of protein coagulum upon the wire throughout the segment it is desirable to attain an even distribution of the wire within the aneurysm. This is greatly facilitated by mounting the two spools upon a geared reel which,

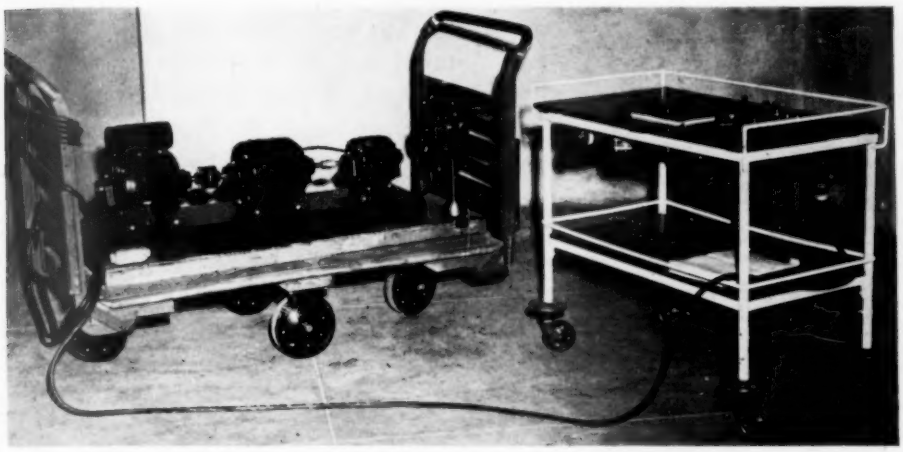

FIG. 2.—Photograph of alternating to direct current converter and heating control panel.

when turned by an assistant during the introduction of the wire, rotates the spools in opposite directions. This, in turn, twists the two wires in opposite directions, forcing them apart upon gaining the inside of the aneurysm. The wire has sufficient expansile thrust when combined with the torque imparted to the wire by the geared reel, to serve to distribute it evenly through the aneurysm.

TECHNIC

Rigid asepsis directed against air-borne as well as direct bacterial contamination must constantly be kept in mind. In cases in which a direct surgical approach is not made to expose the aneurysm, the operation is done under novocaine infiltration anesthesia with roentgenologic guidance. It is now considered best to introduce the needle through a skin incision, using towels over the skin edge held in place by skin clips. All instruments used to this point are discarded and gloves are changed before proceeding with the operation. The special needle (Fig. 1, F), is introduced through the sac wall of the

aneurysm, using the sharp trocar-pointed stylet (Fig. 1, D). The trocar-pointed stylet is replaced by the special inner sheath (Fig. 1, G) bearing a blunt stylet Fig. 1, I). A loop of wire is passed through the wire-passer (Fig. 1, H), which, for the time, is left unattached to the needle. Adequate wire is unwound from the spools mounted upon the geared reel. The loop of wire is then advanced through the needle to a point two or three centimeters beyond the end of the needle. The operator holds one wire and advances the other, thus, forcing the formation of the first loop of wire within the aneurysm. Next, the wire that has been held is gently withdrawn until the bend in the wire snugs-up to the end of the needle. This assures one that the loop thus formed and subsequent loops will land within the sac of a saccular aneurysm. After the passage of several loops of wire by hand, the wire-passer is attached to the needle and the wire quickly passed two wires at a time. The introduction of a ten-meter segment of wire requires about five minutes.

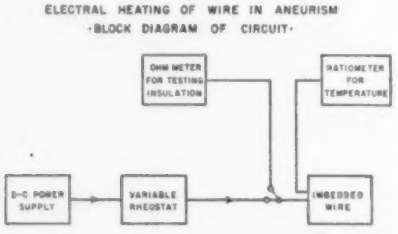

FIG. 3.—Diagram of electrical circuit.

The protruding ends of the wire are attached to the electrode cap (Fig. 1, B) after the latter is adjusted to the needle. It is necessary to remove thoroughly the insulation from the wire in contact with the binding posts of the electrode cap. A roentgenogram of the aneurysm at this point will confirm the position of the wire and reveal the amount of clot already present in the aneurysm, if any. The insulation of the wire is tested before heating, (see ohmmeter, Fig. 3). The rate of blood flow through the aneurysm is next measured by noting the number of amperes required to raise the temperature of the wire 15° C., *i.e.*, an average temperature of 53° C. The wire is finally heated to 80° C. for a period of ten seconds. After an interval the wire may be reheated for another ten-second period. Finally, the wire is clipped flush with the needle and the ends pushed into the aneurysm with a blunt stylet. (Fig. 1, I). Additional segments of wire are introduced and heated until a final ten-meter segment requires three amperes to raise the temperature of the wire to 80° C. Experience has revealed that when one or more segments of wire, well-distributed within a saccular aneurysm, requires only three amperes to heat the wire to 80° C., mass clotting of the aneurysm takes place at once. It has been a routine policy at the final operative stage to check the completeness of clotting by making an arteriogram.

Since the rate of blood flow through aneurysms of similar size may vary as much as 300 per cent, the amount of wire necessary to impede blood flow to a point conducive to mass clotting must likewise vary greatly. Each ten-meter (33-foot) segment of wire has a surface area of eight square inches. The deposit of a layer of protein coagulum by heating increases the surface area to approximately 16 square inches. Some idea of the magnitude of the clot-stimulating surface exposed to flowing blood and the impedence to blood flow effect

may be obtained by multiplying the above figure by ten, the number of ten-meter segments often required to obtain mass clotting in wide-mouth, high rate of flow aneurysms.

Adherence to the wire and to the sac wall of a clot deposited within an aneurysm is imperative and its organization desirable. Whereas wire alone may reinforce blood clot, the heating to 80° C. of wire distributed on the inside surface of an aneurysm sac, as above advocated, causes inflammation in the sac wall. Tissue subjected to a temperature of 80° C. for a few moments reacts within 24 hours with edema, vascular engorgement, and a typical inflammatory reaction on the part of the white corpuscles. The peak of the heat inflammation is reached in from four to six days. This is followed by a period of repair, in which fibroblasts appear and tissue organization takes place with the aid of a network of budding capillaries. The entire reaction occupies a period of from ten to twelve days without, at any time, the appearance of tissue slough. Experimental and clinical evidence suggests that inflammation as engendered by the electrothermic method of wiring aneurysms is an important factor in strengthening the sac wall of an aneurysm.

The electrothermic method has enabled us to attain "brimful" clotting of wide- as well as small-mouth aneurysms. Extensive clotting has been attained in high blood velocity fusiform aneurysms and in a few instances the channel available to blood flow through the aneurysm has been narrowed to approximate the diameter of the parent aorta. A fair number of cases of wide-mouth saccular aneurysms due to syphilis treated by wiring and electrothermic coagulation has now been followed for periods in excess of five years (one case ten years) without showing any return of preoperative symptoms or roentgenographic evidence of increase in size. However, a statement of physical fact was made that "brimful" clotting of saccular aneurysms reduces the strain upon the sac to that resulting from the lateral wall pressure upon the surface area of the mouth of the aneurysm only.

Since the strain is in proportion to the surface area of the mouth, other things being equal, a fully clotted, wide-mouth saccular aneurysm is subjected to a greater strain than a fully clotted, small-mouth saccular aneurysm, and, by the same token, a well, but not completely clotted, fusiform aneurysm is subjected to more strain than a "brimful" clotted wide-mouth saccular aneurysm. As would be expected from these physical facts, our results have indicated that we may expect permanent inactivation in cases of saccular aneurysm belonging to the smaller-mouth group in which "brimful" clotting may be attained (longest follow-up 11 years). Some of the wide-mouth syphilitic saccular aneurysms, however, have remained stabilized for several years, only to manifest evidence of gradual reactivation. A few of these were subjected to another wiring operation with remarkable palliation of symptoms. The wiring and electrothermic coagulation method has given a new lease on life to many cases of fusiform syphilitic aneurysm of the aorta. Many of the cases were stabilized for 4-, 6- and 8-year periods, during which they were in the great part symptom-free from shrinkage of the aneurysms following operation.

Early in our experience with wiring and electrothermic coagulation of the arteriosclerotic fusiform aneurysm of the abdominal aorta we appreciated that less inactivation of the aneurysm resulted from a given amount of clot deposited than obtained in a similarly-treated syphilitic fusiform aneurysm. This lack of resistance to expansion of the aneurysm sac is not unexpected when one considers that arteriosclerotic degeneration is likely to involve the entire thickness of the aorta wall.

FIG. 4.—Roentgenogram of arteriosclerotic aneurysm of the abdominal aorta in a man age 55.

The fusiform aneurysm with the aorta has been occluded with wire, using the method of electrothermic coagulation and endo-arterial occlusion. The collateral circulation is adequate.

Whereas, it seemed certain that clotting the arteriosclerotic fusiform aneurysm down to a narrow channel did slow up the rapidity of growth of the aneurysm, a complete cure could only be counted upon if all blood ceased to flow through the aneurysm. The above conclusion was gradually arrived at through an experience with several cases over a 2- to 4-year period.

As previously stated in our group the arteriosclerotic aneurysm arose from the abdominal aorta some three, or more, centimeters distal to the origin of

the renal arteries in all of the cases examined. This is a fortunate finding because, following wiring with the deposit of clot within the aneurysm, there is one obstacle to hurdle to attain a cure of this vicious lesion, namely, a safe and sure way of occluding the arteriosclerotic abdominal aorta. A critical review of the total surgical experience recorded of ligation of the abdominal aorta prompted the late Dr. Mont R. Reid[1] to state that "partial or gradual occlusion of the aorta by compression (constriction) cannot succeed and should not be attempted. This applies also to the use of partial constrictions proximal to a totally occluding ligature." Brooks, Blalock and Johnson[2] have pointed out that the immediate mortality and incidence of gangrene is so high in humans as to preclude the use of a one-stage occlusion of the aorta.

An experience with some five cases of arteriosclerotic aneurysm in which gradual compression (constrictive) occlusion of the aorta was practised in conjunction with wiring and electrothermic coagulation of the aneurysm convinced me of the wisdom of Doctor Reid's remarks. A possible safe way of securing gradual occlusion of the aorta suggested itself to us in treating four cases of arteriosclerotic aneurysm of the popliteal artery by wiring and electrothermic coagulation. This was before the days of controlled anticoagulant therapy and the wiring method was decided upon because the collateral circulation was poor in these cases. The fusiform aneurysms were gradually and progressively occluded and with them the popliteal arteries, in two or three operative stages, in these four cases without mishap. This experience proved two things: (1) that in the electrothermic method we had a way of obtaining controlled blood clotting; and (2) the impedance effect of wire introduced into the popliteal artery afforded a means of gradual occlusion of the artery from within, without interference with the blood supply to the artery wall.

We thought it fitting to try this principle of endo-arterial occlusion first on a case of arteriosclerotic aneurysm of the abdominal aorta who had restored an essentially normal blood flow through the aneurysm because of cutting through of a cotton tape which had been placed upon the aorta some months previously. Not only had the tape cut through the aorta wall for most of its circumference but there was at the band site a thin-walled aneurysm, the size of a plum. First, a 33-foot segment of insulated wire was introduced into the secondary (traumatic) aneurysm and heated to 80° C. Following this, some 150 feet of No. 34-gauge (B & S) coin silver wire coated with partly hydrolyzed polyvinyl acetate was forced into the abdominal aorta immediately proximal to the beginning of the aneurysm but distal to the origin of the renal arteries. The wire was concentrated in a ball obstructing the aorta to the desired amount using the oscillometer on the leg as an indicator. Partly hydrolyzed polyvinyl acetate coating of the wire was employed primarily for its tissue-irritating effect in stimulating fibroplasia through the meshes of the wire. If this effect is not desired, *e.g.*, in a first-stage partial closure, bare wire may be employed. The combined principle of using unheated wire for gradual occlusion of the aorta immediately proximal to the origin of the aneurysm and

heated (insulated) wire directly in the aneurysm was successfully carried out in this case and it is now some three years since operation. The combined method of endo-arterial occlusion and electrothermic coagulation has now been employed successfully in three cases of fusiform arteriosclerotic aneurysm of the abdominal aorta and two cases of syphilitic fusiform aneurysm of the abdominal aorta. It is unnecessary to emphasize the necessity of using a method of inducing clotting within the aneurysm in which control of the amount of clot induced at a given time is possible. After a thorough investigation of the methods of creating clot-stimulating surfaces upon wire (electrolysis, protein coatings from blood, gelatin, *etc.*), we concluded that electrothermic coagulation, according to the technic described, is the only method which affords selective, controlled clotting within aneurysms. The electrothermic method gives selective clotting following the introduction and heating of a given amount of insulated wire simply because the clot-stimulating protein coagulum is deposited only upon those portions of the wire within the recesses of the sac of the aneurysm. Wire thus located becomes heated and, thus, coated with protein coagulum because it is not exposed to the cooling effect of the faster moving blood in the axial current. This important underlying characteristic of the electrothermic method of wiring aneurysms makes it peculiarly suited to use in combination with endo-arterial occlusion in the gradual obstruction and clotting of the parent artery with the aneurysm in those cases of aneurysm in which sudden occlusion would mean the loss of life or limb.

SUMMARY

Some important differential features in the pathology and symptomatology of aneurysm of the abdominal aorta due to syphilis and arteriosclerosis are brought out in a review of 32 cases. Arteriosclerosis was the cause of the aneurysm in 26 of the 32 cases reviewed.

The importance of pain as a warning of beginning rupture with spreading retroperitoneal hemorrhage in cases of arteriosclerotic aneurysm was emphasized. Attention is called to the fact that there is almost invariably an interval of from two to six days following beginning retroperitoneal hemorrhage before death supervenes from sudden rupture of the retroperitoneal hematoma into the general peritoneal cavity—a period during which life-saving measures may be instituted.

A method of wiring and electrothermic coagulation of aneurysms is presented and discussed. A technic is described for the surgical cure of fusiform aneurysm of the abdominal aorta employing wiring and electrothermic coagulation in conjunction with gradual endo-arterial occlusion.

CONCLUSION

It seems certain, due to the tremendous decrease in mortality from pneumonia and some other diseases, that formerly took great toll in people of the arteriosclerotic age-group, that the surgical therapy of the arteriosclerotic

aneurysm of the abdominal aorta will assume a position of increased importance.

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INTRAVENOUS OXYGEN AND PULMONARY EMBOLISM

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IN A RECENT STUDY by Jacobi, *et al.*,[1] on the effects following the intravenous administration of oxygen to dogs and human beings, it appeared that this form of therapy may have an important place in the treatment of shock. They pointed out that undesirable effects of pulmonary embolism or cardiac tamponade in previous studies were due to the administration of too large a quantity of the gas or to the injection of the gas at too high a pressure. However, in our experience, as reported herein, we could not demonstrate any significant benefit following intravenous oxygen; on the contrary, in some instances definite deleterious effects were noted.

A review of the literature reveals that extrapulmonary respiration was attempted as far back as 1811.[2] Tunnicliffe and Stebbings,[3] in 1916, Singh and Shah,[4] in 1940, injected oxygen intravenously to human beings who were suffering from anoxia of various causes. They reported excellent clinical improvement in each case. Bourne and Smith,[5] in 1927, Dick,[6] in 1929, and Grodins, Ivy, and Adler,[7] in 1943, all administered intravenous oxygen to dogs at various rates. They found that intravenous oxygen caused pulmonary embolism and a distinct arterial hypoxemia. Contrary to these findings, Jacobi described experiments on dogs in shock to whom intravenous oxygen was of distinct benefit. Similarly, he described three human patients in shock who showed marked clinical improvement with intravenous oxygen.

Inasmuch as it appeared possible that intravenous oxygen may be of benefit to patients in shock, it was decided that further study was indicated, especially in regard to the changes in the oxygen saturation of arterial blood.

METHODS AND PROCEDURES

The method used to administer the oxygen was by water displacement of the gas from a gallon container to a wash bottle, and from thence by tubing to the patient. By means of a Murphy-drip system and a water manometer attached to the top of the wash bottle, small but accurate rates of oxygen at known low pressures could be delivered for several hours at a steady flow. A cubital vein was used as the site of the oxygen injection on all patients. Van Slyke gasometric analyses of the oxygen content of arterial blood were done on blood samples drawn from a femoral artery with oiled syringes. At least two samples were drawn for each determination. Hemoglobin determinations were done with a photelometer. Oxygen capacities were calculated therefrom. Blood pressure, pulse, respirations, and hematocrits were recorded at regular and frequent intervals. Electrocardiographic tracings were taken on two

patients, and a series of roentgenograms of the chest on one patient. All these various determinations were done before oxygen was administered and while the gas was given at different rates intravenously. Experiments were conducted on four postoperative patients, all of whom were considered stable from a cardiorespiratory viewpoint. In addition, two patients in shock were also studied. Finally, an *in vitro* experiment was performed in which oxygen was passed through 50 cc. of venous blood at various rates to note any changes in oxygen saturation of the blood.

CASE REPORTS AND RESULTS

Case 1.—Studies were done on four stable, conscious patients. The first of these was a 60-year-old white laborer, upon whom a celiotomy had been performed three days previously. At this time a diagnosis was made of inoperable carcinomatosis of the liver of unknown origin. His laboratory findings included a red blood cell count of 3,600,000; hemoglobin 9.3 Gm.; and total blood proteins 4.2 Gm. per 100 cc. He was afebrile, very jaundiced, and had a pitting edema of his ankles. Blood pressure 105/65, respirations 15, and pulse 72. The arterial oxygen saturation decreased from 94 per cent to 55.5 per cent after the administration of 9.3 cc. of oxygen per minute for 20 minutes. It then further decreased to 46 per cent saturation at the slower rate of 6.6 cc. per minute for 12 minutes. The rate was decreased because of the onset of symptoms which appeared 15 minutes after the patient had received oxygen at the rate of 9.3 cc. per minute. These symptoms consisted of a sensation of pressure in the lower chest, cough, restlessness, and profuse perspiration; some relief was obtained by placing the patient in Fowler's position. Symptoms lasted until 13 minutes after the oxygen was stopped. Respirations increased from 15 to 23; pulse and blood pressure remained constant.

Case 2.—This patient was a 68-year-old colored laborer. A partial gastrectomy for chronic peptic ulcer had been performed five weeks previously. Postoperatively, he developed an abscess and gangrene of the lower lobe of his right lung. At the time of this study, he was afebrile and showed a distinct cyanosis of his lips. His pulse was 78, respirations 20, and blood pressure 120/90. The laboratory findings revealed a red blood cell count of 4,300,000; hemoglobin 13.8 Gm.; and total proteins 5.2 Gm. per 100 cc. His radial and femoral arteries were very sclerotic. The arterial oxygen saturation at the onset was only 77 per cent, which low value we attribute to his lung pathology. He received intravenous oxygen at the rate of 5.5 cc. per minute for 12 minutes and 7.2 cc. for 20 minutes, at which time the oxygen was stopped. The arterial blood sample was taken seven minutes later and was 44.9 per cent saturated. Eleven minutes later it was 57.4 per cent. His symptoms started after he had received 5.5 cc. of oxygen per minute for 12 minutes and 7.2 cc. for three minutes. The symptoms stopped ten minutes after the oxygen was eliminated. They consisted of difficulty in breathing, cough, yawning, feeling of faintness, restlessness, and profuse perspiration. In 15 minutes, these symptoms were followed by clonic contractions of both upper extremities, left facial paralysis, and aphasia. However, he remained conscious. Respirations increased from 20 to 28, and blood pressure from 120/90 to 185/100. The pulse, hemoglobin, and hematocrit all remained constant. There seemed to be some relief of the early symptoms when the patient was placed in Fowler's position.

Case 3.—This patient was a 36-year-old white man, upon whom a palliative gastroenterostomy had been performed for inoperable carcinoma of the stomach six days previous to this study. Examinations of the heart and lungs were negative. The laboratory findings included a red cell count of 4,000,000; hemoglobin 11.5 Gm.; total proteins 6.6 Gm. per 100 cc. The oxygen was administered intravenously at a rate of 4 cc. per minute for 20 minutes, when the arterial oxygen saturation dropped from 87.7 per cent to 75.3 per cent. The oxygen was stopped at this time because of blood clot formation in the needle.

He then received 6 cc. of oxygen per minute for 40 minutes, at which time the arterial blood oxygen saturation was 77 per cent. The rate was then increased to 10 cc. per minute. Eight minutes later, he suddenly commenced to cough, perspired very profusely, and was obviously very apprehensive. He also complained of a feeling of compression about his lower chest. The oxygen was stopped six minutes after the onset of symptoms; at this time the arterial oxygen saturation was 64.2 per cent. All symptoms disappeared 20 minutes after the oxygen was stopped. Pulse, blood pressure, hemoglobin, and hematocrit readings were essentially constant throughout this study. Respirations increased from 25 to 30. Anteroposterior and lateral roentgenograms of his chest, taken before and during the administration of the oxygen, failed to reveal any visible gas bubbles or other changes in the heart or lungs. Electrocardiographic tracings were also recorded before the administration of oxygen, again, at the 6 cc. per minute rate, and, again, ten minutes after the oxygen flow had been stopped. The following deviations from the control electrocardiogram were noted in the latter two tracings: (1) flattening of the T-waves in the first leads; (2) a distinct elevation of the T-wave above the base line in the third leads; and (3) a diphasic T-wave in the fourth leads.

Case 4.—This patient was a white male, age 62. Eleven days previous to this study, a calculus had been removed from the common bile duct and a cholecystectomy performed. His postoperative course was uneventful. The red blood cell count was 4,500,000; hemoglobin 12.8 Gm.; total protein 7.9 Gm. per 100 cc. The electrocardiogram taken prior to surgery and another taken at the onset of the experiment revealed a bradycardia, frequent extrasystoles, and a sinus arrythmia. The arterial blood oxygen saturation at the onset was 91 per cent. It dropped to 83.5 per cent after he had received oxygen 24 minutes at the rate of 4 cc. per minute. The rate of oxygen flow was then increased to 6 cc. per minute. Seven minutes later, the patient suddenly complained of precordial pain. He was restless and perspired profusely. The oxygen was stopped immediately at the onset of his symptoms. Eight minutes later, the arterial blood oxygen saturation had fallen to 65.5 per cent. The precordial pain disappeared shortly after he had received 100 per cent oxygen by mask. The pulse increased from 52 to 66, respirations from 20 to 28, and blood pressure from 90/60 to 100/60 during his symptoms. The hematocrit and hemoglobin values remained constant. Electrocardiograms were taken before and during the administration of the oxygen at rates of 4 cc. and 6 cc. per minute. The following changes were noted in the latter two tracings: (1) flattening of the T-waves in leads I and IV; and (2) elevation of the take-off of the S-T segments in lead IV.

Case 5.—The first attempt to treat a patient in shock occurred when a 52-year-old colored laborer suddenly lapsed into severe shock 12 days following a subtotal gastric resection for carcinoma of the stomach. His condition was evidently caused by the rupture of a lesser omental cavity abscess, although he had had no fever or other clinical signs indicating its presence. When seen by us, plasma had been started. His blood pressure was 80/60, pulse 144, respirations 38. He complained of severe abdominal pain, and the abdominal findings were those of acute diffuse peritonitis. Under cyclopropane anesthesia, his abdomen was opened. At this time, intravenous oxygen was started. No immediate changes were noted. Surgery consisted of attempts to wall-off the abscess with omentum and in draining it. During surgery, the pulse gradually rose to 180, respirations remained constant, and blood pressure fell to 66/50. Immediately postoperative, the patient rallied somewhat, with a blood pressure of 104/58. During this time he received a 500-cc. blood transfusion. He soon, however, lapsed back into his preoperative condition, and progressively declined until his death five hours later. During this last interval, his blood pressure varied from 80/60 to 60/50, his pulse stayed at 155, and respiration at about 52. Except for three short periods of time, intravenous oxygen was given continuously until his death at a rate of 10 cc. per minute. No changes were noted in the patient's condition during these periods. Autopsy revealed a perforated jejunal ulcer, with a generalized suppurative peritonitis, moderate pulmonary edema, and approximately 1 cc. of gas in the right ventricle and 3–4 cc. in the pulmonary artery. The

patient died from the severe toxemia of suppurative peritonitis. In summarizing this case, we feel that the oxygen did not benefit nor, on the other hand, did it appear to be detrimental to him.

Case 6.—The second attempt to treat a patient in shock was made with a 59-year-old colored laborer with an inoperable carcinoma of the head of the pancreas and a complete obstruction of the common bile duct. He received ¼ grain of morphine sulphate and 1/120 grain of atropine sulphate preoperatively. Surgery consisted of palliative cholecystoenterostomy, and entero-enterostomy. The patient left surgery in a state of moderate shock, with a blood pressure of 86/68, pulse 92, and respiration 26. Intravenous oxygen was started one hour later at a rate of 8 cc. per minute; at this time his blood pressure was 89/80, pulse 80, and respiration 28. Five minutes later, the patient became more talkative and seemed somewhat more oriented. The blood pressure rose to 110/80, but the pulse and respiration remained the same. The oxygen was continued for one hour and fifteen minutes, at the end of which time the blood pressure was 110/88, and respiration was 26. In this case, it appears that intravenous oxygen was of benefit to the patient. However, progressive improvement in his postoperative condition was evident before the oxygen was started. During the periods of oxygen administration to both of the last two cases, there was no clinical evidence of pulmonary embolism nor of increased hypoxia. Unfortunately, arterial oxygen determinations were not done in either case.

IN VITRO EXPERIMENT

***In Vitro* Experiment.**—An attempt was made to approximate the amount of absorption of oxygen that occurred in the venous blood during its passage from the intravenous needle to the lungs. Fifty cubic centimeters of venous blood were drawn from a dog with an oiled syringe containing potassium oxalate. The blood was injected under a covering of mineral oil into a 50 cc. burette and a sample drawn from the burette for oxygen determination. Three cubic centimeters of oxygen were slowly injected into the bottom of the burette. The burette was held at such a slant that it took approximately ten seconds for each gas bubble to pass through the blood column to the top of the burette. Blood samples were again drawn, and no changes were noted in the oxygen saturation in this blood. It was observed that the oxygen bubbles rose along the upper surface of the blood column, and, thereby, reduced the amount of gaseous surface exposed to the blood for absorption. This same observation had also been made in several dog experiments in which oxygen was injected into the femoral vein and its passage through the inferior vena cava noted. Here, likewise, the gas bubbles had coalesced and rode along the upper surface of the column of blood.

DISCUSSION.—In experiments on intravenous administration of oxygen to dogs, it had been shown by several investigators that there resulted a fall in the oxygen saturation of the arterial blood. Grodins, Ivy, and others concluded that this hypoxia was due to gaseous pulmonary embolism. In our study of four cases, we, likewise, obtained a consistent fall in the oxygen saturation of arterial blood. This decrease in the oxygen saturation was marked. However, the values are comparable to those obtained in high altitude experiments in which the degree of hypoxemia was correlated with symptoms.[8] We also believe this fall to be due to gaseous pulmonary embolism.

Only a very small part of the gas is absorbed into the blood during the passage of the gas through the systemic veins, heart, and pulmonary arteries. Absorption does not take place because only a very small surface of the gas is exposed to the blood column in the vessels. Moreover, as the oxygen left

the gas bubbles, nitrogen and carbon dioxide would enter the bubble. The pressure of the gases in the bubble is atmospheric, or approximately 760 mm. mercury. The pressure of the gases dissolved in the venous blood is 703 mm.[9] Hence, the bubble of gas would disappear at a rate dependable upon the difference between the gas pressures of 760 mm. and 703 mm. and not upon the difference of pressure between 760 mm. and the pressure of oxygen in the blood (approximately 40 mm.). That the gas bubble may not completely disappear in the venous blood is evidenced by the autopsy performed on the fifth patient who received oxygen intravenously up to the time of his death. One cubic centimeter was found in the right ventricle and 3–4 cc. in the pulmonary artery. The gas had not been absorbed even though it had been in contact with the blood for 2.5 hours following his death, when the heart was opened under water. Still another factor, although minimal, that would diminish the absorption of the oxygen into the venous blood is the higher content of carbon dioxide in this blood as compared to the blood in the pulmonary capillaries.

We feel that oxygen bubbles of fairly large diameter reach and occlude the smaller pulmonary arteries or at least occlude the arterioles. It is unlikely that the pulmonary capillaries are themselves primarily occluded, because if the gas bubbles were small enough to reach the capillaries, their surface exposure would probably be large enough for rapid absorption of the gas by the blood to occur. Moreover, what oxygen was not rapidly absorbed would tend to pass into the alveolar spaces, as the oxygen tension in the gas bubbles would be greater than the 105 mm. oxygen tension in the alveoli. Finally, with a comparison of the size of the pulmonary capillary bed to the small amount of oxygen used in these experiments, it appears evident that occlusion of the capillaries alone would be too minimal to cause the changes noted in the experiments.

Three patients exhibited symptoms of pain in the chest, cough, and restlessness, and the first four patients sweated profusely and had a slightly increased respiratory rate. These symptoms, likewise, appear to be due to pulmonary embolism, for they are exactly analogous to those that occur in the "chokes" of nitrogen pulmonary embolism at high altitudes. That the administration of intravenous oxygen does result in arterial hypoxemia is evident by the consistent measured decrease in the arterial oxygen saturation that occurred in the four patients upon whom these determinations were made. This fall in oxygen saturation progressed as more oxygen was given either at a faster rate or for a longer period of time. That a systemic hypoxia occurred may be evident from the following:

1. Symptoms of cerebral hypoxia occurred in one patient. They consisted of aphasia, facial paralysis, and clonic contractions of his upper extremities.

2. Symptoms of myocardial hypoxia occurred in another patient and consisted of precordial pain.

3. Changes in electrocardiographic tracings occurred in the two patients of whom they were taken. These changes were in the T-waves and the S-T

segments and are comparable to those occurring in the anoxic test for angina pectoris.[10]

The cause of the arterial hypoxemia is apparently pulmonary occlusion. The reflex vasospasm and possibly bronchospasm resulting from the pulmonary embolism may be a further significant factor in the cause of the hypoxia.[11] That this reflex spasm does occur is suggested by the following:

1. The occurrence of vagal stimulation has been shown by the experiments on dogs, in which sectioning of the vagi prevented the shallow rapid respirations that resulted from intravenous oxygen.[7] In our human experiments, vagal stimulation may explain the lack of the increased pulse rate in spite of the presence of hypoxia.

2. That sympathetic stimulation occurs is evidenced by all of the first four patients displaying marked profuse perspiration, and by the fact that the blood pressure either remained constant or became elevated in spite of decreased pulmonary circulation.

3. Cases have been reported in which a small pulmonary embolus produced marked symptoms which were relieved with large doses of atropine and papaverine.

4. Intravenous oxygen was given to one patient for one hour and fifteen minutes at the rate of 8 cc. per minute without the development of any pulmonary or hypoxic symptoms. This patient had been atropinized and was in the state of shock. It is possible that these factors prevented some of the reflex spasm.

SUMMARY

1. Intravenous oxygen was administered to two patients in shock and to four patients who were not in shock, and were considered to be in relatively stable cardiorespiratory condition. Clinical observations alone were made on the last two patients. Clinical and laboratory studies were done on the first four.

2. One experiment was done *in vitro* to approximate the amount of oxygen absorbed by the venous blood during the passage of the gas bubble from the intravenous needle to the lungs.

3. No definite clinical changes were noted in the first patient who was in shock. There was possible clinical improvement that could be attributed to the oxygen in the second patient in shock. Moreover, there was no clinical evidence of pulmonary embolism nor of systemic hypoxia. In the other four patients, there was a marked and consistent decrease in the oxygen saturation of the arterial blood. This decrease was evidenced by actual arterial oxygen saturation determinations, symptoms of systemic hypoxia, and by electrocardiographic changes. Three of these last four patients gave clinical evidence of pulmonary embolism.

4. Studies on the passage of oxygen bubbles through a sample of venous blood at rates comparable to intravenous administration, failed to show any appreciable absorption of the gas by the blood.

CONCLUSIONS

1. The amount of oxygen absorbed by the venous blood from the time of its introduction into the vein until its passage to the smaller pulmonary arteries is insignificant. The gas bubbles coalesce in the veins. Therefore, they are of considerable diameter upon their arrival at the smaller pulmonary arteries, and occlude these vessels.

2. The resulting gaseous pulmonary embolism causes a decreased pulmonary circulation, arterial hypoxemia, and systemic hypoxia. These effects are probably intensified by reflex pulmonary spasm and possibly also bronchospasm.

3. It is possible that some of the ill effects of pulmonary embolism, and thereby arterial hypoxia, may be alleviated by the administration of atropine and papaverine before intravenous oxygen is given. Likewise, a state of shock or of anesthesia may diminish these reflexes and thereby permit the oxygen to be given.

4. In its present status the value of intravenous oxygen as a therapeutic measure is doubtful. Because of pulmonary embolism it is definitely hazardous.

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LARYNGO-ESOPHAGECTOMY

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THE MANAGEMENT of advanced cancer of the larynx presents a difficult and often discouraging problem. Not infrequently these cases are seen with their disease so far advanced that surgery and/or radiation offers palliation for a short time only.

That intrinsic cancer of the larynx will remain localized for many months and even years is well recognized. Yet, when it gets beyond the bounds of its cartilaginous cage it will produce regional lymph node or soft-tissue involvement and even distant metastases.[1] Cancer of the extrinsic larynx usually grows much more rapidly. Often cervical lymph node involvement is the first evidence of the disease. Patients with this advanced disease are seldom operable. If given a course of radiation therapy which is lethal for cancer cells necrosis and slough of both cartilage and soft-tissues may occur.[2]

The patient with extensive intralaryngeal necrosis must have a laryngeal fissure to remove the necrotic material and prevent its aspiration into the bronchial tree. Eventually a majority of these patients die either from recurrent disease, sepsis, pneumonia, pain and inanition, or hemorrhage.[3] Brunschwig[4] recently emphasized these points in describing his procedure for panlaryngectomy.

The case being reported had all these complications, and the patient has now been restored to usefulness and apparent good health.

Case Report.—J. F. M., a 60-year-old white male, was admitted to the Tumor Service, June 10, 1943, with a chief complaint of difficulty in breathing.

Present Illness: Patient had been in excellent health until approximately one year prior to admission, when he began to notice a dull, aching pain in the left side of his neck radiating upward to his left ear. Shortly after this he noticed some hoarseness in speaking. He consulted his local physician who prescribed local medication and sedation, without relief. His hoarseness became progressively worse. During the month prior to admission he experienced difficulty in breathing and some difficulty in swallowing. He had lost approximately 20 to 30 pounds in weight during the past year. Review of his other symptoms revealed nothing of note.

Past Medical and Family History: Irrelevant.

Physical Examination: The patient was a tall, thin, extremely dyspneic white male. There was marked suprasternal retraction with each attempt to inspire. The larynx could not be seen clearly on mirror examination. The entire left larynx was immobile, and there appeared to be a diffuse swelling extending from the base of the epiglottis downward to involve the entire ventricular region, false cord, and partially obscuring the true cord on the left side. No definite ulceration was seen. Crepitation was absent on both sides of the larynx. There was no regional lymph node enlargement. Lungs were clear. Heart was normal size. The rhythm was interrupted by frequent extra systoles. There were no murmurs. Abdomen was flat. Liver was enlarged two finger breadths below the right costal margin. Otherwise physical examination was not remarkable.

Clinical Course: Because of his extreme difficulty in breathing, an emergency tracheotomy was performed. Three days after admission a biopsy, obtained from the region of the left ventricle, showed squamous cell carcinoma, Grade II. At this time a more satisfactory examination of the larynx was possible. The lesion was found to involve the entire left half of the larynx and posteriorly extended to the right. Because of the extent of the disease and probable extension into the esophagus posteriorly, radiation therapy was believed to be the treatment of choice. Between June 10 and August 31 he received 3,550 r. to each of two 6.4-cm. circular ports directed to cross-fire the larynx. Factors: 250 kv., 50 cm. target skin distance 1.5 cu. filter. Patient tolerated his treatment well. Regression of the tumor appeared to be slow. There was rather marked skin

FIG. 1

FIG. 2

FIG. 1.—Patient 24 hours postoperative. Tube for feeding is in upper end of esophagus.
FIG. 2.—Pedicle grafts developed on chest have been shifted to sternoclavicular area. Necrosis in soft-tissue on right side of neck is where common carotid artery perforated.

reaction. On August 13th tracheotomy tube was removed and the stoma permitted to close. Breathing was normal and without difficulty. He was discharged from the hospital on August 13, 1943.

Patient remained symptom-free until October, 1943, when he again reported to the Clinic complaining of difficulty in breathing, cough and pain in his chest. Roentgenograms and physical findings indicated right lower lobe bronchial pneumonia; temperature 103.4° F., pulse 110, respiration 32. Indirect examination showed the larynx to be very edematous. This edema also involved the subcutaneous tissues of the entire neck. Tracheostomy stoma was reopened and considerable purulent material was expelled from the bronchial tree. It was quite evident that extensive necrosis of the larynx had occurred. A laryngeal fissure was performed and the laryngeal cavity packed with iodoform gauze. The patient was given sulfadiazine to control the pneumonia and local infection. From day to day portions of necrotic soft-tissue and cartilage were removed through the laryngeal fissure. After four weeks the patient was relatively symptom-free other than some pain in the left side of his face and in the left temporal region. This pain was not severe enough to interfere with his employment as a gardener. He was discharged.

He again reported to the Clinic, December 22, 1944, complaining of very severe pain in the left side of his head and left neck. Cervical roentgenologic studies showed residual portions of the laryngeal cartilages. Mirror examination showed some slough and necrosis in the epiglottis. Biopsies obtained from the posterior and lateral walls of the tracheostomy stoma revealed extensive recurrent carcinoma. Because of previous extensive radiation therapy the skin was not thought to be able to withstand additional therapy. The extent of disease made surgical extirpation inadvisable. Interstitial radiation with radon was believed the procedure of choice. In divided doses, 21 gold seeds, totaling 19.46 mc., were inserted into the tumor-bearing area. It was believed this additional radiation would produce further necrosis and slough, as the tumor was destroyed. Eighteen days after implanting the last radon, extensive necrosis of the soft-tissues had occurred. Because of the probability of a fatal hemorrhage, a block dissection was believed advisable. On March 22, 1945, the patient was operated upon, under intravenous sodium pentothal anesthesia, and a resection of the residual larynx, cervical trachea, anterior soft-tissues of the neck, and cervical esophagus was performed.

FIG. 3.—Diagram showing attachment of tube-pedicles to neck.

Operative Procedure: Under sodium pentothal anesthesia, an incision was made along the anterior border of the right sternomastoid muscle. By careful blunt and sharp dissection the medial strap muscles were divided below and left attached to the residual larynx and hyoid bone. The right carotid sheath was stripped of all fascia. The dissection extended from the clavicle to one-half inch above the hyoid bone. A similar procedure was followed on the left side; thus, the entire larynx was mobilized laterally. Dissection was then carried across the midline in upper portion, cutting through all fascia and muscles above the hyoid bone. The hyoid bone was divided on either side just anterior to the cornu. The hypopharynx was opened, the mucous membrane of the upper border being clamped prior to cutting to control hemorrhage and prevent retraction. A finger was then inserted through this opening in the hypopharynx into the esophagus. By means of sharp dissection the anterior three-quarters of the cervical esophagus, together with the larynx and trachea was resected from above downwards to approximately one-half inch above the sternum. At this level the trachea and esophagus were amputated. Careful hemostasis was obtained by ligating all bleeding points with No. 000 catgut. The skin was mobilized on either side and sutured with fine black silk over the exposed carotid arteries and internal jugular veins to the small strip of esophageal mucous membrane. The mucous membrane of the anterior hypopharynx was sutured to the skin of the submental region. The trachea was sutured to the skin with interrupted silk sutures. A catheter was then inserted into the esophageal stoma and light dressing applied (Fig. 1). The patient received a transfusion of 500 cc. of citrated blood on the operating table. The operation was well-borne.

Postoperative Course: Patient's postoperative course was complicated by separation of the suture line on both sides, and considerable secondary infection on the right. Healing by secondary intention on the left side was slow, but satisfactory. On the right, the wide separation of the wound edges was followed by some necrosis.

On April 26 and July 12 tube-pedicle grafts were prepared on either side of the chest (Fig. 2). These were to be used to reconstruct the cervical esophagus. On July 22

(three months after his block resection), the right common carotid artery perforated. Fortunately, one member of the Staff was on the floor at the time and immediately ligated this vessel. Ligation was followed by a convulsive seizure which lasted approximately 30 seconds. The patient remained somewhat stuporous for approximately three days. No permanent sequelae resulted from the ligation of this vessel.

By successive steps the tube-pedicles were advanced from chest to the base of the neck on either side of the esophageal stoma, and then advanced to the submental region (Fig. 3). After circulation had been well-established in this area, secondary infection had subsided and wound healing completed, the tube-pedicles were sutured to the neck. An

FIG. 4 FIG. 5

FIG. 4.—Continuity of esophagus has been established. Patient is able to eat a regular diet.

FIG. 5.—Radiograph with barium swallowing shows some puddling in lower portion of artificial esophagus and slight constriction at line of anastomosis.

incision was made on the posterior border of each tube. A corresponding incision was made in the skin on either side of the neck and adjacent surfaces were sutured with interrupted fine black silk. Healing of these anastomoses was prompt and complete. On January 17, 1946 the clavicular portions of the tube-pedicle grafts were freed on either side and brought across the midline. The muscle and mucous membrane of the esophageal stoma was opened and the cut-end of the pedicle sutured to the upper end of the esophagus. Healing of this anastomosis was satisfactory. On March 14 an incision was made along the adjacent surfaces of the tube-pedicles. The tubes were opened; the skin was undermined and corresponding edges approximated. The inner surfaces were sutured with interrupted mattress sutures of plain No. 0 catgut to form the lining of the reconstructed cervical esophagus. The external surfaces were approximated with interrupted sutures of fine black silk. The healing of the two grafts was rather slow and complicated by slight superficial infection in the midportion, which subsided under penicillin therapy. On the 5th postoperative day the patient was taking liquids, and on the 20th postoperative

day he was able to swallow a regular diet (Figs. 4 & 5). Patient is now employed as a farm laborer. He has gained 37 pounds in weight and appears to be free of disease.

COMMENT: Resection of the cervical esophagus and larynx for cancer of the cervical esophagus is an accepted procedure. Block resection of the structures of the neck bounded by the carotid arteries laterally and the cervical vertebrae posteriorly is a more extensive procedure. It is justified when one considers the hopelessness of the condition being treated. Its use must be limited to patients in whom no wide extension or distant metastasis can be demonstrated. During the past year three other patients with similar stages of disease as the patient reported in this paper were seen in the clinic. One refused further surgery after his left common carotid artery had been ligated to control hemorrhage. The second case had a fatal hemorrhage the week before this operative procedure was to be performed. At autopsy, the disease in both was found to be localized to the neck and grossly would have been entirely included within the operative field. The third case has recently been resected. Reconstruction of the removed portion of his esophagus will be performed.

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LEIOMYOMA OF THE KIDNEY

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The discovery of a large retroperitoneal mass in infancy and childhood leads one immediately to a consideration of the two most common lesions in that age-group, namely, neuroblastoma and Wilms' embryoma of the kidney. The literature of surgery, pediatrics, urology and pathology is replete with case reports and discussions of these interesting conditions.[5, 6, 7] Occasionally, however, the surgeon is surprised to find a benign tumor in a case in which the preoperative diagnosis was that of malignancy, as in the case of a leiomyoma of the kidney in a newborn child, the subject of this paper. In an examination of such standard texts as Ladd and Gross,[1] Campbell,[2] and Brennemann,[3] the reader will find no mention of leiomyoma of the kidney, and Ewing[4] dismisses the subject with the statement that "in the kidney, small myomata and myolipomas occur in capsule or cortex and appear to be derived from fragments of capsule tissue."

Leiomyomata of the kidney in older age-groups have been reported on rare occasions from time to time, and, in general, may be said to consist of three types:

1. Small, frequently multiple myomata, several millimeters in diameter, found beneath the kidney capsule or in the superficial cortex. They are encountered as purely accidental findings at autopsy in individuals who have died from other causes.

2. Large solitary growths causing symptoms and discovered during the life of the individual.

3. Myomata which appear to be malignant or have undergone definite sarcomatous changes.

Cases of the first variety have been reported by Busse,[11] Lartigau and Larkin,[13] Hess,[15] Hallas,[16] and Kretschmer.[20] The first recorded case of the second category was that of a large myoma of the renal hilus reported by Schluter,[8] in 1890. Four years later, Regnier[9] presented a myoma of the renal capsule, and Reverdin[10] described a 48-pound fibromyoma of the fatty capsule of the kidney. In 1899, Busse reported a large fibromyoma, and Ochsner[12] demonstrated a case of leiomyofibroma of the kidney weighing 4,600 Gm., and consisting mostly of fibrous tissue. In 1914, Hoffman[17] reported a case of leiomyoma of the kidney in a woman, age 35, and 14 years later, Bugbee[18] described a leiomyoma of the kidney in a woman, age 35. The tumor was 13.5 cm. in its longest diameter, appeared beneath the renal capsule, and was sharply circumscribed and enveloped in a thin fibrous capsule. Crosbie and Pinkerton,[21] in 1932, reported a large, encapsulated, lobulated leiomyoma

in a woman, age 35. The tumor seemed to arise from the outer wall of the pelvis but eventually became imbedded in the kidney substance. In 1935, Heggie and Alstead[25] described a tumor 6.5 x 5.5 x 3.75 inches in a woman, age 40. It was well-encapsulated and the blood vessels, present in moderate amount, were well-formed. The authors surmised that it might have arisen from a small tumor beneath the capsule, but in its advanced growth, the origin could not be stated definitely. Counseller and Menville,[30, 31] in 1936, described a case in a woman, age 29. The tumor was associated with benign cysts in a kidney with duplicate pelves. In 1937, Michon[28] added a case of angiofibroleiomyoma, and Marion[27] a case of angiomyoma. In their report, Bailey and Harrison[32] included a leiomyoma weighing 4,940 Gm. and measuring 38 x 24 x 11 cm. This tumor occurred in a woman, age 26. In 1939, Gordon, Kimmelstiel and Cabell[33] described the youngest case yet on record, a girl age 15, in which the tumor was like a myoma of the uterus. The last recorded case was that of Crabtree,[34] in 1944, who described a leiomyoma of the kidney with cystic degeneration and calcification in a male, age 39.

Several malignant muscle tumors of the kidney have been reported. Jacobaeus,[14] in 1903, described multiple angiosarcomas of the kidney in a case of tuberous sclerosis, and Hallas,[16] in 1912, recorded a fibromyo-endothelioma that had metastasized to the aortic lymph nodes, in the capsule of a woman, age 59. Berry,[19] in 1929, reported a leiomyosarcoma of the kidney in a woman, age 26, which had a well-defined capsule in some places and not in others, and which, on microscopy, showed the capsule to be split in places. In 1933, Cooke[22] reported a malignant leiomyoma which had replaced the right kidney in a woman, age 60, and Swan[23] described a leiomyosarcoma of the left kidney removed from a male, age 71. In his series of tumors, Smith[24] included one case of leiomyosarcoma of the kidney. In 1937, Mintz[26] contributed two cases of leiomyosarcoma, and Patch[29] a case of malignant leiomyoma.

The case we are presenting is unique even in so rare a tumor as leiomyoma of the kidney. It is the first recorded case of a large solitary leiomyoma of the kidney in a newborn child.

Case Report.—Baby S. was born on July 17, 1946 at the Beth El Hospital, a full-term, white male infant, delivered by low forceps application. The delivery was uneventful and the baby began to breathe spontaneously. His birth weight was six pounds and six ounces, and his length 20.5 inches. He was the third child born of this mother, the other two children being normal in every respect. There was no history of neoplasia in the family.

Immediately after delivery, it was noted that the baby's abdomen was somewhat enlarged, and examination revealed the presence of a large abdominal tumor. The patient was transferred from the nursery to the Pediatric Service for further study.

Examination showed a full-term, alert, vigorous male infant, who was somewhat pale. Temperature 98° F. The baby was normal in all respects except for the abdominal mass. The abdomen was soft, and no fluid was detected. The mass filled the left side of the abdomen, extending from the left costal margin to the left iliac crest and from the midline to the left loin. The tips of the fingers could just be placed beneath the left lower ribs and the upper margin of the mass. The surface of the tumor was perfectly smooth and its consistency firm. There was apparently no tenderness on palpation and the mass

was mobile, as could be demonstrated by pushing it forward from the loin. Its anterior border in the midline was round and smooth, but the posterior border could not be detected. The liver and spleen were not palpable, nor was the kidney on the right side. Micturition and defecation were normal and urinalysis revealed no abnormalities. The blood count was: R. B. C. 5,790,000, Hb. 119 per cent (18.3 Gm.); W. B. C. 9,600. No erythroblasts or pathologic cells were found on blood smear. The blood sugar was 82 mg. per cent, and the blood urea was 9.4 mg. per cent. An intravenous pyelogram, using six cubic centimeters of diodrast, was done. Roentgenograms revealed the presence of a large mass in the left abdomen (Fig. 1) which displaced the intestines and colon upward and to the right. The right kidney was normally visualized. The pyelographic outline on the right side appeared normal. The left kidney outline was not identifiable. A speck of contrast medium appeared in the region of the left kidney pelvis, and the kidney appeared to be displaced upward and to the right. The impression was that of the presence of a left kidney neoplasm.

FIG. 1.—Pyelogram of kidneys. Note displacement of left colon. Arrow indicates contrast medium in left pelvis.

The child did well on an evaporated milk formula and, July 29, 1946, operation was performed (I. C. Z.). Under drop-ether anesthesia, the abdomen was opened through a left upper rectus muscle-splitting incision extending slightly below the umbilicus. On entering the peritoneal cavity, a large retroperitoneal mass on the left side presented itself. This mass pushed the left colon toward the midline and the spleen upward. The liver was grossly normal. The right kidney was palpated and found to be normal, but the left kidney could not be identified. The mass was the size and shape of a baseball, smooth and very firm. The left lateral peritoneum was incised and the retroperitoneum entered. The tumor was found to be wel-circumscribed and was easily shelled out except medially where a pedicle was encountered. This pedicle consisted of the ureter and renal vessels which were not invaded by the tumor mass. They were ligated individually, following which the tumor was easily removed. The nephric space was packed with thrombin-fibrin foam because of a slight generalized ooze. The lateral peritoneum was sutured and the abdomen closed in layers, without drainage.

Immediately following the operation, the infant was given a blood transfusion and fluids by scalp vein. Postoperative recovery was complete in 24 hours. The baby ran an unexplained low-grade fever for two weeks, but he ate well and was alert and normal in all his reactions. He was discharged, August 24, 1946, weighing seven pounds and eight ounces, and in good condition. Recent examination of the child has shown that he is progressing well.

Pathologic Report.—Gross: The specimen consists of an ovoid firm mass, measuring 7x5x5 cm., to one pole of which is attached a small infantile kidney which measures 3.5 cm. in its greatest diameter. The mass is encapsulated by a thin, delicate fibrous capsule.

It blends imperceptibly with the renal tissue near the hilus but otherwise appears to be fairly well demarcated from the kidney. The mass is uniformly firm throughout (Figs. 2, 3 and 4). On section, the cut-surface (which had been previously fixed in formalin) presents the so-called classical watered silk appearance of a uterine myoma. Small vascular spaces are identified in many portions of the tumor. There is no hemorrhage or necrosis. The renal tissue present in the specimen does not appear grossly abnormal.

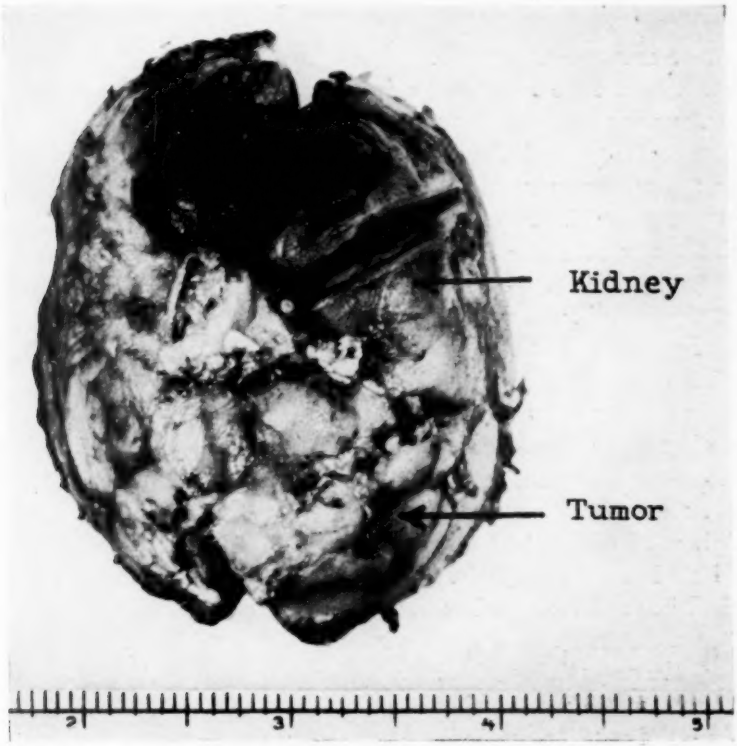


FIG. 2.—Gross appearance of unopened specimen.

Microscopic: A fairly-well demarcated but encapsulated tumor is present. At the periphery of the tumor small bands of neoplastic tissue infiltrate among the cortical tubules and glomeruli with extension to the subcapsular region. In one section the renal pelvic epithelium is well preserved. The tumor tissue is composed of compact bundles of elongated cells containing vesicular ovoid nuclei which show a tendency to clubbing at their extremities. No mitotic figures are observed. Abundant fibrillar intercellular material is present. The bundles of tumor tissue show a fasciculated appearance. Prominent throughout the tumor are small vascular spaces lined by flattened endothelial cells and containing a few erythrocytes (Figs. 5, 6 and 7). *Pathologic Diagnosis:* Cellular leiomyoma of the kidney.

DISCUSSION.—As previously mentioned, leiomyomata of the kidney may be either of the small, multiple, symptomless variety discovered as incidental findings at autopsy or large solitary tumors recognizable during the life of the individual and productive of symptoms. The histogenesis of these tumors is

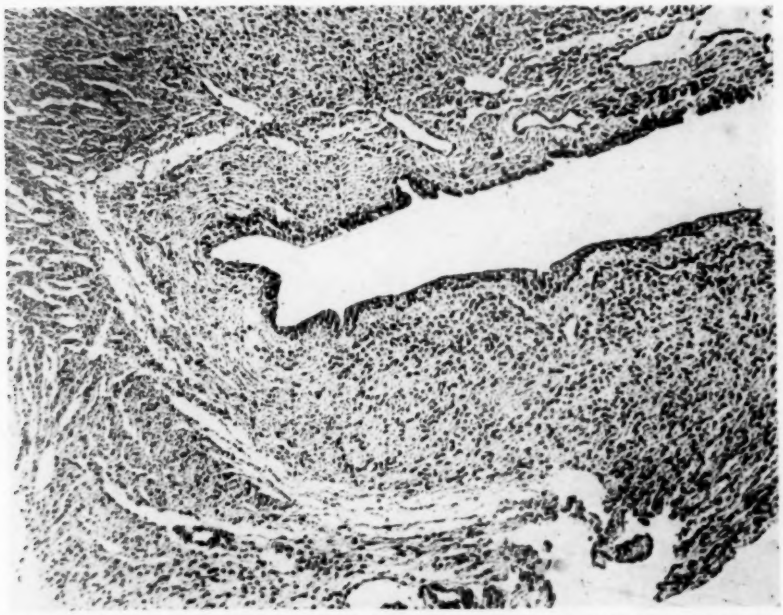
FIG. 3

FIG. 4

FIG. 3.—Gross appearance of opened specimen.
FIG. 4.—Gross appearance of tumor. Note watered silk appearance of myoma.

of considerable interest. Smooth muscle fibers can be found normally in the capsule of the kidney, the kidney pelvis and calices, and the renal vasculature.

FIG. 5



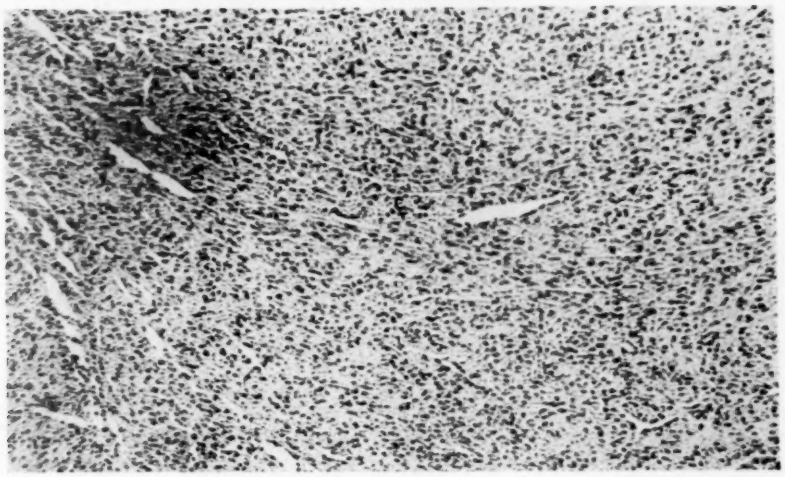


FIG. 6

FIG. 5.—Low power microscopic appearance of tumor. Note epithelium of kidney pelvis.

FIG. 6.—Low power microscopic appearance of tumor. Note vascular spaces.

They are not found in the parenchyma of the kidney. Busse[11] has described abundant muscle fibers in the medulla of the embryonic kidney. This he claimed

to be a possible source of fibromyomas of the kidney. This observation has not been confirmed by others, and smooth muscle fibers have not been seen outside of the walls of blood vessels in the medulla of the embryonic and fetal kidney (Gordon).[33] The discovery of small myomata of the cortex in those cases in which the tumor does not appear to be in continuity with the renal capsule can be explained as being choristomas or hamartomas. In the case described by Gordon, *et al.*,[33] the outstanding microscopic feature of the tumor was the presence of numerous large blood vessels, giving one the impression that the

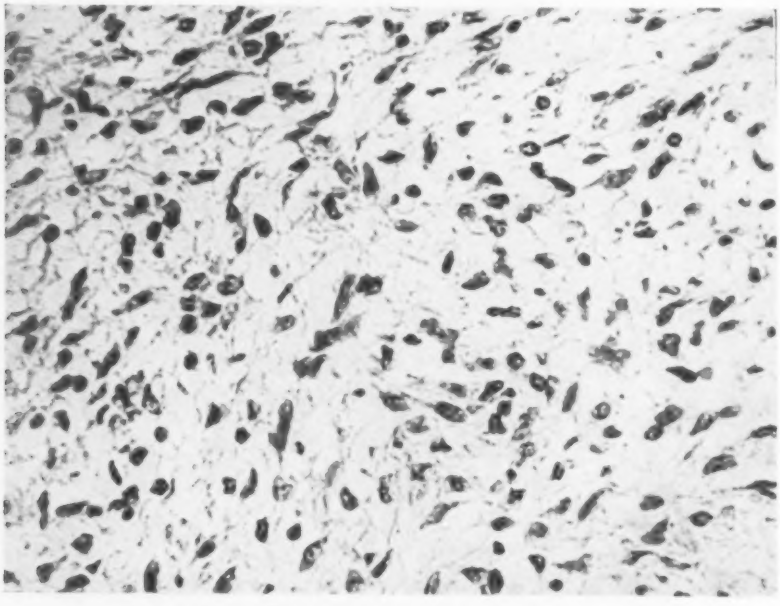


FIG. 7.—High power microscopic appearance of tumor.

tumor was derived from the muscular coats of these vessels, the young muscle fibers arising from the outer and middle coats of the arterial walls. In view of the fact that the main characteristic of the tumor was the formation of large muscular arteries, the authors believed that the proper description for this case was arterioleiomyoma of the kidney.

Some writers (Busse, Hallas, Heggie and Alstead, Hess, Hoffman, Lartigau and Larkin, Michon, Regnier and Reverdin) have expressed the opinion that these tumors arose from the renal capsule, while others (Bailey and Harrison, Counseller and Menville, Crosbie and Pinkerton, and Mintz) believe the origin to be from the renal pelvis or calices. Rubaschow,[35] describing similar lesions of the epididymis, ventured the opinion that they might arise from embryonic rests of the primitive myotome. Oberndorfer,[36] discussing similar lesions in the epididymis, was convinced that a chronic inflammatory process was the most important etiologic factor. There is little evidence, however, to support this view.

Unfortunately, in most cases of large solitary tumors, the advanced growth of the mass precludes any attempt to ascertain its exact origin. In the case here reported, origin from the capsule can be ruled out by the gross relationship of the tumor to the remaining renal tissue. The inclusion of well-defined small vasculature spaces in many sections of the neoplasm suggests derivation from vasculature smooth muscle. However, no definite transition from discrete blood vessel wall to neoplastic muscle could be identified, so that a definite statement concerning histogenesis is impossible.

Clinically, leiomyomata of the kidney present several interesting features. In view of the paucity of reported cases of large myomata of the kidney, generalizations are out of the question. The tumors have previously been found in an age-group varying from 15–71 years, and by far the greater number have been found in women. Both kidneys have been found to be equally involved. The conclusion of Crabtree[34] that leiomyomata of the kidney have a tendency to be associated with renal cysts is not borne out by a review of the literature. Grossly, these tumors have the consistency of hard rubber and on section, present a smooth, white glistening appearance. They are usually well-circumscribed and enclosed in a fibrous capsule. They are of slow growth and present few signs other than a mass and occasionally pain or discomfort. Hematuria is rarely seen, and dysuria and frequency are occasional complaints. Fever, when it occurs, is usually the result of infection of the urinary tract or gross degeneration of the tumor. If sufficiently large so that the calices or pelvis are encroached upon, the pyelogram is of diagnostic value, but, even then, there is no means of distinguishing it from other renal tumors. In the absence of malignant changes, the prognosis of leiomyomata of the kidney following nephrectomy is good, and if malignant change does occur, there seems to be little tendency to invade surrounding tissues.[31] The procedure of choice in the treatment of this condition is nephrectomy.

SUMMARY

1. The literature of leiomyoma of the kidney is reviewed.
2. A case of large solitary leiomyoma of the kidney in a newborn child is reported.
3. The histogenesis of the condition is discussed.
4. The clinical aspects of the lesion are presented.

The authors wish to express their thanks to Dr. Nathan Mitchell, pathologist of the Beth El Hospital, for his intensive study of the surgical specimen.

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CONGENITAL ABSENCE OF GALLBLADDER

REPORT OF THREE CASES

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IT IS QUITE STRIKING that congenital absence of the gallbladder without other anomalies of the biliary system should be so rare, whereas other anomalies of the biliary system are present in 10 per cent of autopsy cases.[1] Courvoisier[2] collected 25 such cases in 1890. In 1928, Bower[3] reviewed the literature and found 31 cases; the earliest of these cases having been reported by Bergman in 1701. Gross,[4] in 1938, published 38 cases. In 1945, Dixon and Lichtman[5] reviewed 50 cases since 1900, and reported ten additional cases. Our review of the available literature revealed 71 such cases. To this number we wish to add three case reports.

The incidence of congenital absence of the gallbladder is about 0.065 per cent, as calculated from 18,350 autopsies by Talmadge.[6] Kirshbaum[7] reported the incidence of such anomaly to be about one case in 3,661 (0.03 per cent); while Smith, Hall, Mentzer, and Nägel found six cases (0.075 per cent) in 7,919 autopsy specimens.

Syphilis, catarrhal inflammation of the biliary tract, fetal peritonitis, maternal toxins, and mechanical factors all have been advanced by various authors as theories of origin of this anomaly. A more easily defended theory involves the embryology of the biliary tree. The embryologic origin of the biliary tract is intimately associated with that of the liver. The entire biliary system, including the liver, arises as a ventral outgrowth from the gut entoderm in the region of the anterior intestinal portal.[8] From the floor of the future duodenum arises the hepatic diverticulum; a cranial portion which is the anlagen of the bile ducts, and a caudal portion which is to become the gallbladder and cystic duct. Though the hepatic diverticulum is originally tubular, the biliary passage tends to become solid, and it is not until the seventh week that a lumen has been reëstablished throughout most of its length. Thus, failure of the gallbladder anlagen to form, or, as Gross[4] suggests, failure of the solid anlagen to become tubular, would result in an absent gallbladder. Miller[9] presents strong evidence that the lumen may sometimes fail to form; as he demonstrated tubular tissue in the hepatoduodenal ligament.

In our review of the literature we found many case reports to be incomplete and a few were available to us only in abstract form. An analysis of the data with respect to age and sex, symptoms, preoperative diagnosis, whether found at operation or autopsy, and attempts to prove an intrahepatic gall-

bladder was made. This material was obtained from a total of 71 cases, 34 of which were reported from surgical procedures while 38 were autopsy reports—one case appearing in both series.

The average age of all cases reported was 46 years at the time of discovery. Females were twice as frequent as males in the entire series. These figures agree with those of Melville.[10] However, when viewed as to autopsy or operative reports, the ratio in autopsied specimens is one to one; while those operated upon have a three and three-tenths to one ratio. This would tend to show that occurrence of the anomaly has little relation to sex; but that symptoms provoking exploration of the biliary tree in this entity follow the same sex ratio as does all surgical biliary disease.

Of the 71 cases 34 gave histories indicating biliary tract disease. Due to the brevity and incompleteness of the earlier reports, this analysis is not necessarily valid.

Of the 34 cases (Table I) operated upon, the preoperative diagnosis in 13 cases was cholecystitis; in eight it was obstruction of the common bile duct; five cases were listed only as exploratory celiotomies; four were found incidental to operations for nonassociated intra-abdominal pathology; and in four cases a preoperative diagnosis was not recorded.

In the series upon whom operations were performed, the gallbladder was reported as absent in all 34 cases, while the cystic duct was reported absent only 15 times. Twenty-one reports noted the condition of the common duct; it being dilated 11 times, containing stones in 11 and appearing normal in seven. The liver was described 13 times. In three cases it was atrophic, in two, hypertrophic, and in two reports anomalies were cited—one being a large Riedel lobe and the other a complete absence of the left lobe.

In the series where the gallbladder was found to be congenitally absent at postmortem examination (Table II), the cystic duct was recorded as absent in 18 cases; the common duct as dilated in four cases, containing stones in only one case; and as normal in seven instances. Ten cases exhibited a pathologic liver, seven of the atrophic variety, and three of the hypertrophic type. Four reports noted anomalies of the liver. In two the quadrate lobe was indistinct; while in a third case the quadrate lobe was absent. The remaining case exhibited nonseparation of the liver lobes.

Visualization of the gallbladder by cholecystograms was attempted in 12 instances. In several patients the attempt was repeated using different methods of administration of the dye. All failed to be visualized.

In one autopsy specimen (Mackmull[11]—1930) and two postoperative patients (Drenckhahn and Rogers[12]—1943; and Dixon and Lichtman[5]—1945), the biliary trees were injected, *via* the common duct, with radiopaque material in an attempt to visualize an intrahepatic gallbladder if present. All failed to reveal a shadow which could be interpreted as a gallbladder.

CASE REPORTS

Case 1.—Mrs. R. A., a 52-year-old white female, was admitted to Wesley Memorial Hospital, September 13, 1945, because of severe cramping pain in the epigastrium, nausea,

TABLE I

SYNOPSIS OF CASES OPERATED UPON

Author		Age and Sex	Symptoms and Duration Of		Preoperative Diagnosis	Why Operated	Findings at Surgery	Proven Not Intrahepatic-
Bower	1928	50 F.	Severe pain in R. U. Q. Jaundice.	1 day	Acute pancreatitis; perforated ulcer	Acute abdomen.	Absent gallbladder. Left liver lobe absent.	No.
Danzis	1935	53 F.	Belching, with vomiting postcibal. Pain in R. U. Q. radiating to back.	3 mos.	Cholecystitis, with calculi.	Cholecystectomy.	Absent gallbladder and cystic duct. Com. duct dilated and containing stones, with inspissated bile.	Proven at autopsy. Death from peritonitis.
Davis	1944	56 F.	Anorexia, nausea, abdominal pain.	5 days		Celiotomy	Absence of gallbladder and cystic duct. Liver normal.	No.
Dixon & Lichtman	1945	(1) 61 F.	Jaundice, chills, fever, and pain in L. U. Q. Postcibal distress.	8 yrs.	Cholecystic dis., with biliary obst.	Biliary disease	Absent gallbladder and cystic duct. Stones in dilated com. duct. Liver normal.	No. Neg. X-ray.
		(2) 68 M.	Jaundice, chills, fever, and epigastric pain. Weight loss of 60 lbs.	6 wks.	Obst. Cholecystic disease.	Biliary disease.	Absent gallbladder. Com. duct normal. Liver normal. No stones.	No. Neg. X-ray.
		(3) 29 F.	Chills, fever, epigastric pain. Vomiting or eating relieved pain.	4 yrs.	Perforating gastric ulcer.	Acute abdomen.	Gallbladder absent. Com. duct normal.	No.
		(4) 39 F.	Nausea, vomiting, food intolerance, and right-sided pain.	3 yrs.	Susp. gallbladder disease.	Biliary disease.	Gallbladder and cystic duct absent. Com. duct moderately dilated.	No.
		(5) 53 M.	Bloating and tenderness R. U. Q.	10 yrs.	Duod. ulcer and cholecystic dis.		Absent gallbladder. Com. duct normal.	No.
		(6) 52 F.	Jaundice, chills, fever, nausea, vomiting. Intolerance to foods. Colicky R. U. Q. pain.	4 yrs.	Cholecystitis, with cholelithiasis.	Biliary disease.	Absent gallbladder. Normal com. duct. Liver normal.	No. Neg. X-ray.
		(7) 57 M.	Jaundice, chills, fever, nausea, vomiting. R. U. Q. pain.	12 yrs.			Absent gallbladder and cystic duct. Com. duct and liver normal. Lymphosarcoma of stomach.	No.
		(8) 50 F.	Jaundice, food intolerance, pruritis acholic stools, epigast. pain.			Celiotomy.	No gallbladder. Com. duct dilated. Hepatitis. Duod. distended.	Neg. X-ray. Retrograde study revealed no G. B.

TABLE I – *Continued*

SYNOPSIS OF CASES OPERATED UPON

Author		Age and Sex	Symptoms and Duration Of		Preoperative Diagnosis	Why Operated	Findings at Surgery	Proven Not Intrahepatic–
Drenckhahn & Rogers	1943	43 F.	Postcibal burning, with bloating. Food intolerance.	10 yrs.	Chronic cholecystitis.	Biliary disease.	Gallbladder and cystic duct absent. Liver grayish-brown with fibrous markings. Com. duct moderately dilated.	Neg. X-ray, Retrograde study revealed no G. B.
Emmert	1931	20 F.	Pain in right abdomen.	3 yrs.	Appendicobiliary synd.	Biliary disease.	No gallbladder. Normal ducts. Liver enlarged and red.	No. Neg. X-ray.
Ewers	1914	45 F.	Pain in hypogastrium.			Exp. appendicectomy.	Gallbladder and cystic duct absent. Panc. head enlarged and hard.	No.
Fowler	1917	42 F.	Jaundice.		Com. duct obst.	Biliary disease.	No gallbladder or cystic duct. Panc. hard and indurated.	No.
Golob	1927	59 F.	Belching and epigast. pressure. Pyrosis.	4 yrs.	Cholecystitis.	Biliary disease.	Gallbladder not located.	No. Neg. X-ray
Giuliani	1924	35 F.	Sympt. of common duct obstruction.		Com. duct obst.	Biliary disease.	Gallbladder absent. Stone in com. duct.	No.
Hinder	1909	60 M.	Jaundice and dyspepsia. Apparent cholecystitis.			Acute abdomen.	No gallbladder or cystic duct. Pancreas hard.	No.
Ishiyama	1927	50 F.	Jaundice. Pain in R. U. Q.	20 yrs.	Com. duct obst.	Biliary disease.	Gallbladder absent. Com. duct enlarged, with stones. Liver swollen and icteric.	No.
Leopold	1911	45 F.	Jaundice. Gallstone colic.		Cholecystitis, with stones.	Biliary disease.	Absent gallbladder. Stones in common duct.	No.
Lintz	1927	48 F.	Pain in R. U. Q. radiating to back.	5 yrs.		Biliary disease.	No gallbladder. Large Riedel lobe.	No. Neg. X-ray.
Melville	1937	48 F.	Epigastric pain. Jaundice and obst. symptoms. Vomiting.	7 yrs.	Chronic cholecystitis.	Biliary disease.	No gallbladder located.	No. Neg. X-ray.
Meyer	1929	21 M.	Subicteric sclerae. Epigastric distress and colicky pain.	5 yrs.	Cholecystitis.	Biliary disease.	Absent gallbladder. Band between usual G-B site and duodenum.	No. Neg. X-ray.

TABLE I—*Continued*

SYNOPSIS OF CASES OPERATED UPON

Author		Age and Sex	Symptoms and Duration Of		Preoperative Diagnosis	Why Operated	Findings at Surgery	Proven Not Intrahepatic-
Naegeli	1921	65 F.	Gallstone colic. Vomiting. Icterus.	30 yrs.			No gallbladder or common duct. Liver cirrhotic.	No.
		34 F.	Vomiting, jaundice, acholic stools. Pain in R. U. Q.	5 yrs.			No gallbladder. Stone in common duct. Com. duct dilated.	No.
Niemach	1908	60 F.	Nausea, vomiting, chills, fever. Abd. pain. Acholic stools.	2 wks.	Com. duct obst.	Biliary disease.	Gallbladder absent. Stone in common duct.	No.
Robertson, Robertson, & Bower	1940	45 M.	Postcibal distress. Jaundice and acholic stools.	2 yrs.	Cholecystitis and com. duct obst.	Biliary disease.	Gallbladder and cystic duct not identified. Dense adhesions about gallbladder area.	Yes, at autopsy.
Sarma	1941	41 F.	Abd. pain and vomiting.	3 mos.	Cholecystitis.	Biliary disease.	Gallbladder absent. Liver small, with dense adhesions.	No. Neg. X-ray.
		47 F.	Typical gallbladder symptoms, with calculi.		Cholecystitis, with calculi.	Biliary disease.	Absent gallbladder and cystic duct. Com. duct dilated, with stones.	No Neg. X-ray.
Schmidt	1928	30 F.	Pain in epigastrium.	6 yrs.	Cholelithiasis, with pericholecystitis.	Biliary disease.	Gallbladder and cystic duct absent. Common duct normal.	No.
Schulz	1914	64 F.					Absent gallbladder and cystic duct. Com. duct dilated, with stones.	No.
Stone	1908	54 F.	Jaundice and epigastric pain.	5 yrs.	Cholelithiasis.	Biliary disease.	Gallbladder absent. Hepatic and com. ducts dilated, with stones.	No.
Torrence	1920	38 M.	Digestion poor, with constipation. Chronic appendix symptoms.	3 yrs.	Appendicitis.		Absent gallbladder and cystic duct.	No.
Whipple	1921	52 F.	Nausea, vomiting, jaundice, pruritis. Bloating and belching postcibal. Epigastric pain.	2 yrs.	Obst. of com. duct.	Biliary disease.	Gallbladder and cystic duct absent. Com. duct markedly dilated, with stones. Pancreatic lymphangitis.	No.

vomiting, jaundice, and clay-colored stools. The pain had been present for one week, radiating through to the back and up to the right shoulder. It was not related to meals nor foods and was relieved only temporarily by hypodermic injections of opiates. Nausea and vomiting were persistent. Jaundice appeared three days after the onset of pain. She had noted clay-colored stools for two days prior to entry into the hospital. Similar episodes, though less severe, had occurred once ten years ago and again one month prior to her hospital admission.

Physical examination revealed a well-nourished white female appearing moderately ill and having a marked icteric tint to her skin and sclerae. The heart was not enlarged but there were frequent extrasystoles and a systolic murmur was present at the apex. Pulse 68; blood pressure 104/65. Examination of the abdomen revealed no scars, rigidity or masses. Tenderness on deep palpation in both upper quadrants was present.

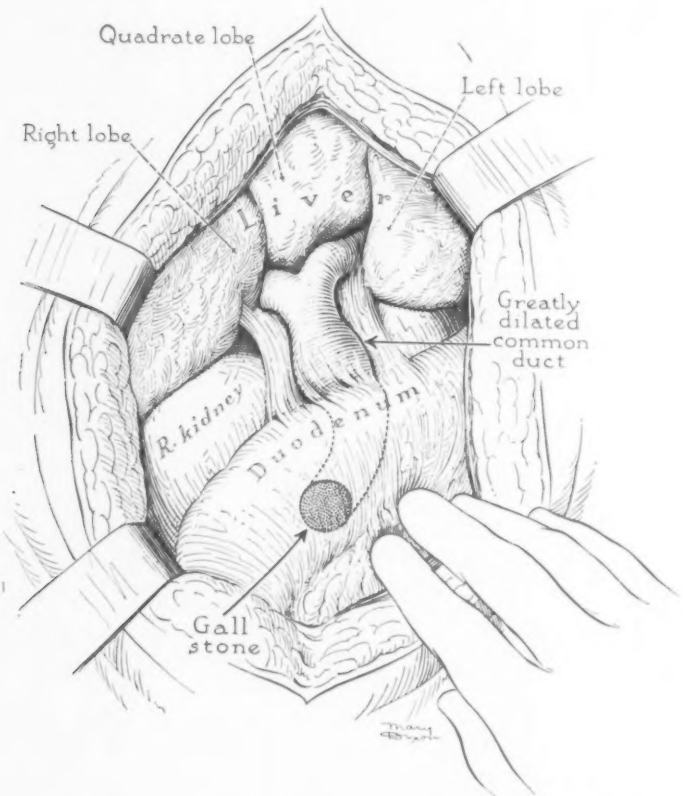

FIG. 1.—Case 1: Drawing of findings at time of operation.

The erythrocyte count was 5,790,000 cells per cm., the hemoglobin 15 Gm. per 100 cc. of blood; and the white cell count was 5,800 cells per cm. Urinary urobilinogen was absent, while bile was present in the urine; otherwise the urine was normal. The icteric index was 123.5 units, and the van den Bergh test revealed a prompt direct reaction with a 9.45 mg. per cent quantitative indirect reaction. The stools were clay-colored and contained no bile. The blood proteins on admission were 6.80 Gm. of total protein per 100 cc., with 3.87 Gm. albumin fraction and 2.93 Gm. globulin fraction. An intravenous

TABLE II

SYNOPSIS OF CASES AUTOPSIED

Author		Age and Sex	Symptoms Presented	Autopsy Findings	Proven Intrahepatic	Remarks
Arnissat	1831	24 yrs. F.	Abdominal-chest disease.	Gallbladder absent; cystic duct present. Pancreas enlarged.	Autopsy only.	
Baker	1835	Nm.	Suppurative process.	Gallbladder absent; cystic duct not mentioned.	Autopsy only.	Additional information about symptoms not given.
Bergman	1701	Nm.	Not mentioned.	Gallbladder absent; numerous small cystic ducts. Liver showed two lobes not separated.	Autopsy only.	
Bergman	1836	60 yrs. F.	Mental disease.	Liver enlarged. Gallbladder replaced by small fibrous mass.	Autopsy only.	This case is questionable, as gallbladder may have been present.
Bubenhoefer	1905	66 yrs. M.	Cardiac failure.	Gallbladder and cystic duct absent. Liver small and cirrhotic.	Autopsy only.	
Canton	1847	65 yrs. F.	Cerebral hemorrhage.	Gallbladder and cystic duct absent. Liver two-thirds normal size. Common duct twice normal size.	Autopsy only.	
Danzis	1935	53 yrs. F.	Belching, with vomiting postcibal. Pain R. U. Q. radiating to back.	No evidence of gallbladder. No cystic duct found. Common duct dissected back into hepatics and liver.	Autopsy only.	Death following operation.
Droste	1853	74 yrs. F.	Pulmonary disease.	Gallbladder absent. Cystic duct not mentioned. Liver atrophic.	Autopsy only.	
Eiben	1910	48 yrs. M.	Pneumonia.	Gallbladder and cystic duct absent. Common duct not dilated. Normal liver.	Autopsy only.	
Eiben	1910	20 yrs. F.	Tuberculosis.	Gallbladder and cystic duct absent.	Autopsy only.	
Elvert	1780	Nm.	Not mentioned.	Gallbladder absent. Cystic duct not mentioned	Autopsy only.	

TABLE II—*Continued*

SYNOPSIS OF CASES AUTOPSIED

Author		Age and Sex	Symptoms Presented	Autopsy Findings	Proven Intrahepatic	Remarks
Eschner	1894	2 yrs.	Pulmonary signs and symptoms of ricketts. No biliary disease.	Gallbladder absent.	Autopsy only.	
Gaultier	1829	60 yrs. M.	Pulmonary tuberculosis.	No gallbladder. Cystic duct entered liver.	Autopsy only.	Cystic duct was traced into liver substance.
Gordon & Dragutsky	1942	76 yrs. M.	Urinary complaints. Anorexia, with constipation.	Gallbladder absent. No cystic duct. Common duct one cm. in diameter.	Multiple microscopic sections of liver.	
Harle	1856	50 yrs. F	Not mentioned.	No gallbladder or cystic duct found.	Autopsy only.	
Hoffman & Jackson	1910	65 yrs. F.	Pneumonia.	No gallbladder or cystic duct found. Common duct dilated.		
Kehr		Adult M.	Not mentioned.	Absent gallbladder. Cystic duct unusually large.	Autopsy only.	Cystic duct present and enlarged.
Latham	1897	49 yrs. M.	Pulmonary tuberculosis.	Gallbladder absent.	Autopsy only.	
Lenain	1853	74 yrs. F.	Pulmonary disease.	Gallbladder and cystic duct absent.	Autopsy only.	
Lockhart	1927	24 yrs. F.	Symptoms of lung abscess.	Only pouch of common duct at level of gallbladder site.	Autopsy only.	Outpouching of common duct present.
Loreta	1888	40 yrs. F.	Not mentioned.	No gallbladder or cystic duct found.	Autopsy only.	
Knox	1922	1 yr. F.	Bronchopneumonia	Absent gallbladder.	Autopsy only.	
Mackmull	1930	57 yrs. M.	Pulmonary tuberculosis. Constipation with attacks of nausea.	Gallbladder and cystic duct absent.	Retrograde lipiodol injection of liver.	Retrograde examination of the biliary tree with X-ray carried out in cadaver.
Miller	1936	84 yrs. M.	No gastro-intestinal or biliary complaint. Myocardial failure.	Absent gallbladder. Small, blind cystic duct in fibrous tissue. Quadrate lobe of liver indistinct.	Autopsy only.	Remnant of cystic duct present.
Montault	1829	Adult M.	Carcinoma of pylorus.	Absent gallbladder and cystic duct. Liver atrophic.	Autopsy only.	

TABLE II—*Continued*

SYNOPSIS OF CASES AUTOPSIED

Author		Age and Sex	Symptoms Presented	Autopsy Findings	Proven Intrahepatic	Remarks
Möller	1920	28 yrs. F.	Bronchopneumonia	Absent gallbladder and cystic duct. Common duct normal.	Autopsy only.	
Patterson	1864	35 yrs. M.	Asthma death.	No gallbladder or cystic duct present. Liver hypertrophic.	Autopsy only.	
Robertson & Robertson & Bower	1940	45 yrs. M.	Indigestion, with postprandial burning. Jaundice and clay-colored stools.	No gallbladder or cystic duct located. Common duct dilated. Cirrhosis of hypertrophic type. Carcinoma of common duct.	Autopsy only.	Operated for removal of common duct obstruction.
Sands	1865	29 yrs. M.	Pulmonary tuberculosis.	Absent gallbladder. Liver atrophic. Absent quadrate lobe of liver.	Autopsy only.	
Schachner	1916	2 yrs.	Not mentioned.	Absent gallbladder. Syphilis of liver.	Autopsy only.	
Tambault & Schachman	1882	Nm.	Paretic dement. No gallbladder symptoms.	Gallbladder absent. Liver small.	Autopsy only.	
Talmadge	1938	51 yrs. M.	None.	Gallbladder absent. Small cystic duct present. Hepatic and common ducts dilated. Liver normal but quadrate lobe poorly developed.	Careful dissection of liver and biliary system.	
Trimble	1850	55 yrs. F.	Infectious disease, with jaundice.	No gallbladder or cystic duct. Liver atrophic. Pancreas contained stone.	Autopsy only.	
Vergne	1826	26 yrs. M.	Accidental death.	Absent gallbladder and cystic duct.		
Konjetzny	1913	64 yrs. F.	Attacks of gallstone colic. Died from perforation.	Absent gallbladder. Stone in common duct.	Autopsy only.	
Dixon	1945	74 yrs. M.	Epigastric distress. Diabetes. Hemochromatosis.	Gallbladder absent. Com. duct normal. Liver normal.	Autopsy only.	
Dixon	1945	38 yrs. M.	Generalized miliary tuberculosis.	Gallbladder and cystic duct absent. Liver normal. Common duct normal.	Autopsy only.	

liver function test revealed only 0.3241 Gm. of hippuric acid recovered, compared to 0.5 Gm., or more, for the normal. This figure indicates considerable liver damage—a conclusion supported by gross examination of the liver at operation. The electrocardiogram, taken September 14th, showed changes interpreted as minimal evidence of myocardial damage. A plain film of the abdomen revealed no evidence of opaque biliary calculi. The right diaphragm was elevated. An upper gastro-intestinal tract roentgenologic study revealed no evidence of intrinsic pathology.

With a provisional diagnosis of cholelithiasis and obstruction of the common duct, the patient was prepared for operation. The preoperative management consisted chiefly

FIG. 2.—Cholangiogram of Case 1.

NOTE: The roentgenogram has been retouched for sake of clarity. The extra coil of the external limb of the "T"-tube has been obliterated.

of a high carbohydrate-high protein-low fat diet plus ten mg. daily of intramuscular vitamin K. Following this regimen the patient's prothrombin time was 24 seconds, the control being 25 seconds.

On September 22nd, using spinal anesthesia, the patient was operated upon. The liver was atrophic, nodular, yellow-brown in color, with streaks of scar tissue between the nodules. No gallbladder could be seen. The stomach was normal, as was the head of the pancreas. The duodenum was adherent to the liver and common duct. The common duct was markedly enlarged, being approximately three centimeters in diameter (Fig. 1). "White bile" was obtained from the common duct by aspiration. A large

stone, approximately two centimeters in diameter, could be palpated in the region of the ampulla of Vater. The extrahepatic ducts were thoroughly searched, but no structure resembling a gallbladder or cystic duct was discernible.

The stone was removed, and a "T"-tube inserted into the common duct after carefully probing the right and left hepatic duct.

A cholangiogram, October 3, 1945, showed the common duct to be patent, as the radiopaque material flowed into the duodenum. No structures resembling cystic duct or gallbladder were seen (Fig. 2). The patient was discharged from the hospital on the 17th postoperative day, having made an uneventful recovery. Following removal of the "T"-tube, cholecystography was attempted by the oral method, on November 23rd, to further rule out the possibility of an intrahepatic gallbladder, but no such structure was visualized.

Case 2.—Through the courtesy of Dr. J. A. Shacter, we are reporting a second case of congenital absence of the gallbladder. On March 20, 1946, Mrs. M. P. entered Wesley Memorial Hospital complaining of pain in the right upper quadrant, and an intolerance to greasy foods. These symptoms had been constantly present during the past three years, but the patient also stated that even as a small child she was unable to eat the high-fat diet of her family table. The pain began as epigastric distress gradually increasing in severity. The onset was in the late evening with the pain lasting 12 to 48 hours. Bicarbonate of soda gave only partial relief. Nausea, belching, and flatulence accompanied these episodes. A weight loss of ten pounds in the past six months was noted. The past history revealed an appendicectomy had been performed in 1928. The patient had been pregnant 13 times, and had been delivered of six living children. On physical examination, this 62-year-old white woman appeared to be in no apparent distress. Blood pressure 140/90; normal pulse. A few small, nontender lymph nodes were palpated in the left submaxillary area. The heart was of normal size, shape, and rhythm. The abdomen was obese, with a right lower quadrant scar. There was no tenderness or rigidity; and no masses or viscera were palpable.

The urine was normal. The erythrocyte count was 4,710,000 cells per cm., and the hemoglobin was 14 Gm. per 100 cc. The leukocyte count was 6,050 cells per cm.; and the blood Wassermann was negative. An oral hippuric acid test was within normal limits. The nonprotein nitrogen was 44.7 mg. per 100 cc. of blood. The total proteins were 7.05 Gm. per 100 cc., with the albumin and globulin fractions 3.70 Gm. and 3.35 Gm., respectively. Cholecystograms, made elsewhere, failed to visualize the gallbladder. The prothrombin time was within normal limits.

A preoperative diagnosis of chronic cholecystitis was made, and the patient operated upon on March 25, 1946. Careful inspection of the entire inferior surface of the liver failed to reveal a gallbladder. A small accessory liver lobe, 5 x 4 cm., was found at about the normal site of the gallbladder. The entire inferior and superior surface of the liver was readily palpated. Inspection of the liver surface itself failed to reveal what might have been a gallbladder buried within the liver substance. No cystic duct was found. Since the common duct was not opened, a "T"-tube was not utilized in an attempt to visualize an intrahepatic gallbladder.

Case 3.—Mrs. M. W., a patient of Dr. Paul Rhoads and Dr. Arthur Metz, entered Wesley Memorial Hospital May 16, 1946. She complained of yellow color of the skin, intense itching, nausea, and malaise, all of four weeks duration. Although she had been troubled with "biliousness" for many years, the first right upper abdominal colic occurred in May, 1938. This episode subsided, and the patient was symptom-free until April, 1946, at which time a painless jaundice was noticed. The inventory of systems revealed selective dyspepsia to fatty foods, clay-colored stools, and dark-colored urine.

On physical examination, this 60-year-old, white female, appeared deeply jaundiced and superficial excoriations of the skin were noted. Except for an old right lower quadrant scar (removal of suppurative appendix and drainage of abscess in 1938), the only positive physical findings were those mentioned above.

The laboratory reported a normal blood count and hemoglobin level. The urine was dark in color, with urobilinogen present on several occasions. The stools were clay-colored and positive for occult blood. The icteric index was 148 units, with a four plus prompt van den Bergh reaction. On admission, the prothrombin time was 50 seconds, with 25 seconds for the control. Following vitamin K therapy the prothrombin returned to 20 seconds, with a control of 20 seconds. The albumin-globulin ratio was reversed. An upper gastro-intestinal study revealed no intrinsic pathology, and the electrocardiogram was within normal limits.

A preoperative diagnosis of neoplasm involving the extrahepatic biliary system was made. At operation, May 23rd, a thorough search failed to reveal a gallbladder or cystic duct. The extrahepatic ducts were slightly enlarged and very firm, as if invaded by a new growth. The pancreas appeared normal except for evidence of passive congestion. The surgical impression was primary neoplasm invading the common and hepatic bile ducts. Absence of the gallbladder and cystic duct was a coincidental finding. Since the common bile duct was not incised, cholangiograms were not possible.

COMMENT: For evident reasons, a preoperative diagnosis of congenital absence of the gallbladder is extremely difficult, if not impossible. This fact is well illustrated in our survey by the ratio of cases found at autopsy to those discovered at surgery. There is no group of symptoms or signs which are of value in making such a diagnosis. Roentgenographic visualization of the biliary tract is the most accurate diagnostic method known at present. The accuracy of this test, when properly conducted, is about 90 to 95 per cent.[13] However, when this method fails to produce any shadow whatsover, congenital absence of the gallbladder is so rare that such a condition is not suspected, there being no reported case of the diagnosis made before operation or postmortem examination.

Should surgical procedure fail to reveal the gallbladder in or about its normal location, the presence of an intrahepatic location of this viscus should be ruled out. This can best be done, we believe, by retrograde cholangiography. Such procedure was reported in only three cases in the literature. Mackmull[11] injected a cadaver specimen; while Drenckhahn and Rogers,[12] and Dixon and Lichtman[5] illustrated the use of this method in the patient. This procedure of retrograde visualization of the biliary tree was carried out in one of the cases satisfactorily, and no evidence of the gallbladder or cystic duct was seen. Kehr mentions needling the liver and aspirating bile as proof of an intrehepatic viscus. We agree with Talmadge[5] who contends that aspiration of bile from the liver does not prove the presence of an intrahepatic gallbladder, inasmuch as bile may be aspirated from a dilated intrahepatic bile duct.

SUMMARY

1. The literature pertaining to congenitally absent gallbladder is reviewed.

2. A total of 71 cases of congenital absence of the gallbladder were reviewed and analyzed; 34 at operation and 38 at autopsy—one case appearing in both series.

3. We present three additional surgical case reports of congenital absence of the gallbladder. The absence of an intrahepatic gallbladder was proven by cholangiography in one case.

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THE EFFECT OF ROTATION ON THE CIRCULATION OF THE LOWER EXTREMITIES

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EXPERIMENTS IN AVIATION MEDICINE with the "human centrifuge" produced marked changes in cardiovascular function. This suggested that centrifugal force might be used to drive blood through partially occluded arteries, and so increase the circulation to the lower extremities in cases of peripheral vascular disease. This was discussed with Mr. Caleb Smith, an engineer and inventor of Seneca Falls, N. Y., and he agreed to build the necessary apparatus for us to test this hypothesis.

METHOD

The apparatus consisted of a chair (Fig. 1), revolved by a 1 H.P. electric motor, and a Worthington "all-speed" drive, so that the speed could be varied from 0 to 60 RPM. Construction was such that the pivot could be released to balance the subject under static conditions by means of counterweights. This gave dynamic balance during rotation. It is apparent that in such a centrifugal force experiment the column of venous blood will be acted upon by the same force as the arterial supply, with resultant venous stasis and increased capillary pressure. If this persists, it may result in the accumulation of extracellular fluid. To counteract venous pooling, the chair was made to tip at rest, so that the feet might be elevated (Fig. 2), thus, alternating a period of rotation with one of elevation.

Dizziness was an obvious disadvantage of such a procedure, so, to minimize it, the head was placed at the pivot point, and the mechanism was designed to control the rate of acceleration and deceleration.

It was difficult to decide how to test for circulatory change under the conditions of such an experiment. Plethysmographic measurements would record only volume changes, which might be misleading due to venous stasis. Capillary microscopy appeared impractical. Temperature readings during rotation presumably would be altered by air currents and the cooling effect of evaporation of sweat. It was felt, however, that if significant changes were produced, they could be recorded by skin temperature readings taken before and after rotation. A "dermatherm" wire thermocouple was used for these.

Preliminary experiments to determine the optimum conditions, such as speed of rotation, time of rotation, time of elevation of extremities, degree of nausea and vertigo, and effect of air cooling on the exposed foot were carried out. It was found that covering the foot with an oilskin bag during rotation produced no significant change; hence, this was omitted in later runs.

Two sets of experiments were undertaken. In the first, the subject was rotated at 36 and at 48 RPM for one minute; the chair was tilted up after each

rotation, and skin temperatures recorded at minute intervals thereafter. In the second series, the subject was alternately rotated at 48 RPM for two minutes and his legs elevated for one minute for a total of five times.

Skin temperature readings were taken from the plantar surface of the great toe in the first series and, in addition, from the plantar surface of the foot in the second series. The room temperature was kept constant at 68°–70° F. The 17 tested subjects were normal young males.

RESULTS

In five cases the subjects were unable to tolerate the procedure, and the number of alternate rotations had to be reduced accordingly. In the first series

FIG. 1.—The revolving chair used in experiments to test the effect of centrifugal force on the peripheral circulation. The centering of the head over the pivot, the counterweights, and the driving mechanism are shown.

a slight increase in skin temperature was noted in four runs, and a slight decrease in two. With alternate rotation and elevation the temperature of the great toe increased slightly (1.6°C. or less) in five tests and decreased slightly (2.3°C. or less) in four, while the foot temperature increased (3.3°C. or less) in seven and decreased (1.5°C. or less) in two.

Nausea and vertigo were, as expected, found to be functions of the rates of acceleration and deceleration. In all cases these symptoms were present to a greater or lesser degree, and in five subjects it was necessary to curtail the experiment for these reasons. Foot cramps and tingling were common complaints, which were thought to be due to venous stasis or the presence of extracellular fluid. There were two cases of frank edema. In the first the subject

was unusually tall (6 ft. 4.5 ins.) and, hence, was subjected to increased centrifugal force, while in the second case, the subject was spun for ten minutes continuously.

The pulse rate, taken during and after rotation, did not reveal constant or unusual variation.

COMMENT: It is apparent from these results that significant temperature changes were not produced by the methods employed. This is interpreted to mean that no appreciable increase occurred in the circulation. The vasomotor effect of labyrinthine reflexes, or apprehension, may have played a part but were

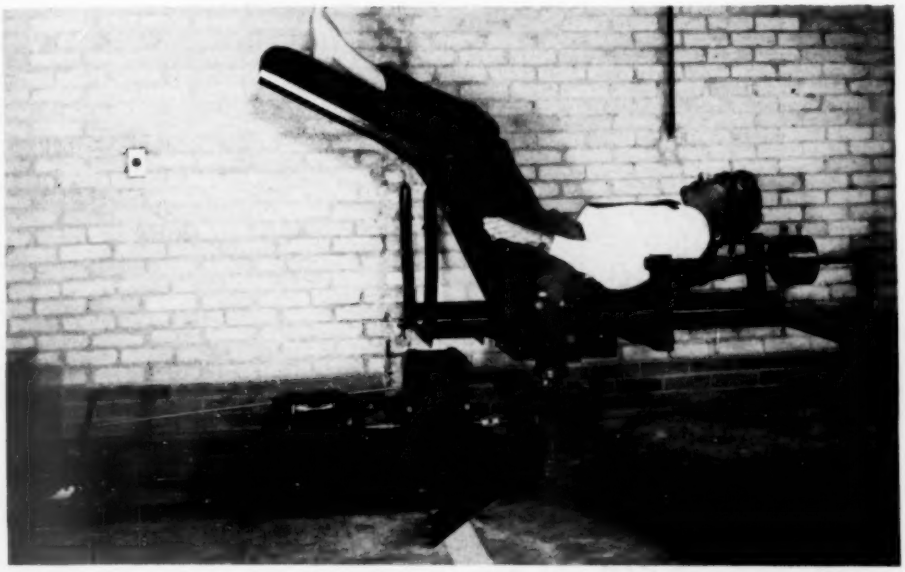

FIG. 2.—The chair tilted back so that the feet may be elevated. The usual sequence was a period of rotation at 48 RPM for two minutes, alternating with one minute of elevating the feet at rest, to avoid venous pooling.

not apparent. The occurrence of edema was obviously undesirable. In view of this, and other disagreeable side effects, and with negative results, it was deemed unwise to subject patients to the procedure. It is recorded only in order that others may be spared the expense and trouble of testing the hypothesis.

SUMMARY

Subjects were rotated in a specially designed revolving chair for varied periods and at varied RPM for the purpose of determining the effect of centrifugal force on the circulation of the lower extremity as measured by change in skin temperature.

The results obtained reveal that no significant improvement of the circulation of the lower extremity is produced by this method. This, combined with the undesirable side-effects of vertigo, nausea, and occasional edema of the extremities, makes it unsatisfactory for clinical trial.

SPONTANEOUS ILEOCOLIC FISTULA: A COMPLICATION OF CARCINOMA

CASE REPORT

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ENTEROCOLIC FISTULA is an uncommon, but not rare complication of carcinoma of the gastro-intestinal tract. A review of the literature reveals that most cases[1, 2, 3] were studied either late in the progress of the disease or at autopsy. The present case is reported to show that this complication may occur while the patient is still operable, a point brought out in recent reports by Catell and Mosely.[4]

Fistula formation, acute or chronic, may be produced by various etiologic factors. The more common is the benign ulceration as seen in the gastrojejunocolic fistula. A second etiologic factor is trauma, due either to operation or to accidental injury. Carcinoma of the large bowel, a third factor, characteristically invades all layers, including the serosa. The neoplasm may then extend directly into any adjacent organ, ulcerate and, thus, form a fistula. On the other hand, the ulceration may first occur in the carcinomatous lesion causing a slow perforation. An adjacent organ, such as the ileum, may then form a block for the perforation. The ulceration continues and the neoplastic tissue invades the small bowel, thus, forming a malignant ileocolic fistula.

One of the outstanding findings in the study of these cases has been the occurrence of a distinct anemia. Barker and Hummel,[5] in a detailed study of macrocytic anemia in association with intestinal strictures and anastomosis concluded that the disease is a distinct entity and not a simple coincidence of "idiopathic" pernicious anemia and an intestinal lesion. They suggest the pathogenesis to be intimately bound up with stasis and putrefication of the intestinal contents resulting in absorption of toxic substances. Surgical removal results in a cure, but intensive liver therapy may bring about clinical and hematologic improvement in some cases.

Roentgenologic examinations appear to be the most effective and reliable means of detecting the lesion. In many cases a routine study of the upper gastro-intestinal tract will not reveal any defect. In most instances the barium enema is most conclusive, and it is suggested that the insufflation of air into the colon or the double contrast enema be used.

The following case of spontaneous ileocolic fistula caused by carcinoma of descending colon is presented:

Case Report.—J. C., a 47-year-old white male, entered the Veterans' Hospital, Rocky Hill, Conn., June 18, 1946, complaining of "pain beneath his shoulder blades and attacks of rectal bleeding and diarrhea" of approximately nine months' duration. He had

FIG. 1.—Roentgenogram illustrating the direct anastomosis between the descending colon and ileum. Diverticula of the descending colon are noted at the site of the anastomosis.

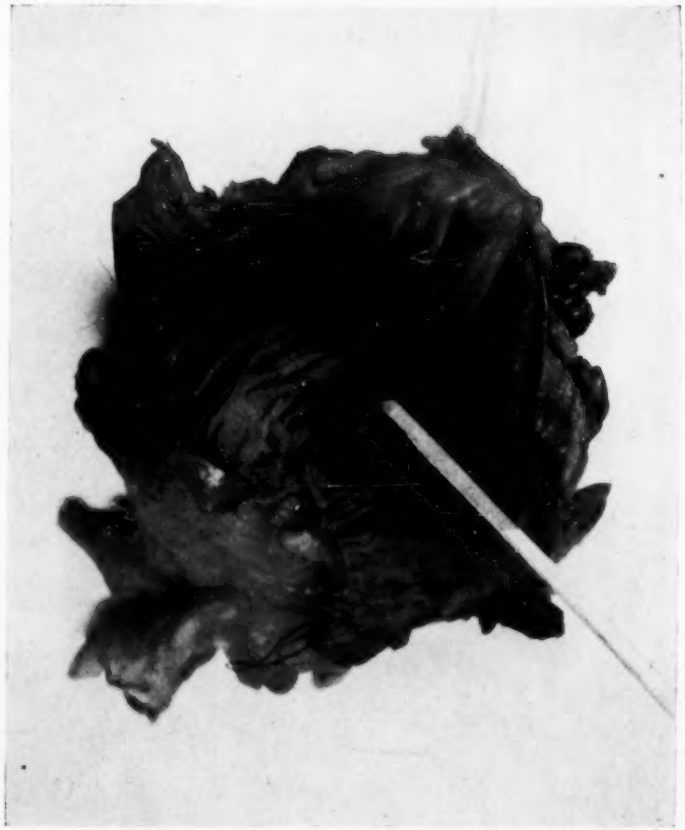

FIG. 2.—Specimen removed at operation—combined resection of ileum and colon for ileocolic fistula complicating carcinoma of the colon. The probe is inserted into the fistula through the ileal opening. Note the size of the opening and the border of neoplastic tissue.

lost 45 pounds, felt dizzy and weak, and had slight dyspnea. Seven months before admission, a gastro-intestinal series and an air enema had been done by his local physician. Diverticula of the colon were found and it was thought, at that time, that the diverticula caused his bleeding and diarrhea. His past history was essentially negative except for an appendicectomy performed in 1942.

Physical examination on admission revealed a thin, poorly nourished white male. There was a marked pallor to his skin, but his cheeks were flushed. On palpation, there

FIG. 3.—Same specimen as Figure 2, showing the probe inserted into the fistula through opening in the descending colon.

was a suggestion of a mass in the left side of the abdomen, but this was difficult to evaluate because of the tenderness and pain of which the patient complained. The examination was otherwise normal.

Laboratory Data.—Urinalysis—negative. Mazzini—negative. Sputum—negative. Daily blood counts revealed a macrocytic hypochromic anemia, with an average of 2.9 million red blood cells, and 45 per cent hemoglobin.

Roentgenologic Findings.—Examination revealed a neoplasm in the region of the middle third of the descending colon. There was a direct communication between large and small bowel at the site of the obstruction (Fig. 1).

Preoperative Treatment.—1. Whole blood transfusions (five). 2. Concentrated vitamins intramuscularly. 3. High protein (Amigen), High carbohydrate diet. 4. Iron and liver therapy. 5. Sulfasuxidine. 6. Purgatives and cleansing enemata. 7. Miller-Abbott tube passed before operation.

Operative Findings and Technic.—(Figs. 2 and 3): At operation (7-30-'46) a large mass was found at the midportion of the descending colon. A loop of ileum was intimately attached to the large bowel. These lay parallel and were bound together in a side-to-side pathologic anastomosis, measuring 2 cm. in diameter. Exploration revealed no other gross findings of note. The lesion was removed *in toto* to preserve the anastomosis. Bowel continuity was reëstablished by a side-to-side anastomosis of the ileum and an end-to-end anastomosis of the descending colon. A complementary cecostomy was performed. Postoperatively, the patient was given sulfadiazine and penicillin.

The microscopic report (Fig. 4) was that of adenocarcinoma of the large bowel Grade II, with extension into the ileum, and the formation of a pathologic anastomosis. The lymphatics sectioned showed no tumor cells.

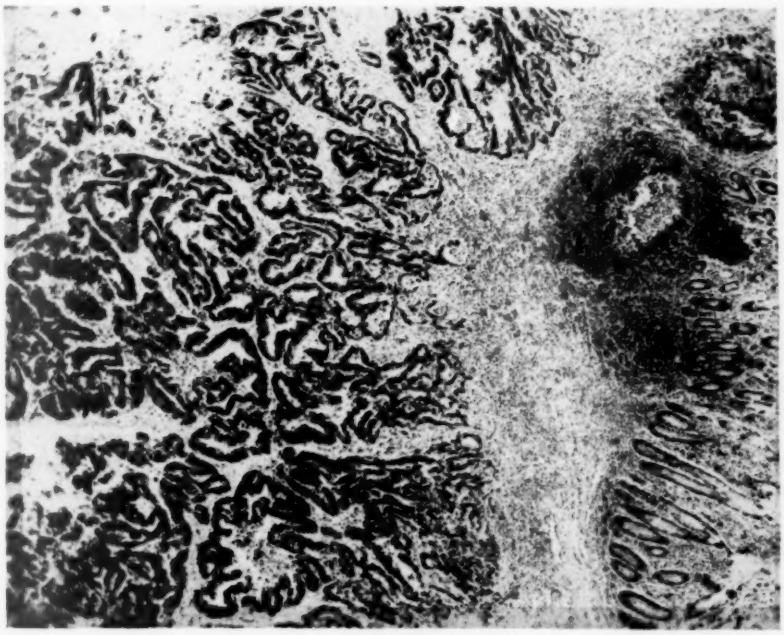

FIG. 4.—Microphotograph of block of tissue taken from the border of the fistula, showing normal ileal mucosa at the right, with invasion of neoplastic glands from a primary adenocarcinoma of the colon. (Hematoxylin and eosin stain x 125).

Progress.—The postoperative course was uneventful except for a small amount of drainage from a fecal fistula, which cleared up in a short time. Three and one-half months following operation he had gained 18 lbs.; his hemoglobin was 82 per cent, and red blood count 4.42 million. On the most recent follow-up note, 11-12-'46, he states that he has no complaints and is doing part time work.

The patient reported to us June 10th. His weight is 190 lbs. The blood count is 5,000,000 red blood cells and hemoglobin 90 per cent. A repeat G. I. series was performed and showed no abnormal findings. He has no complaints and is back to full time work.

COMMENT: There are several interesting findings in this case. Whereas, a review of the literature would lead one to expect a macrocytic hyperchromic type of anemia, this patient presented a macrocytic hypochromic type. The

explanation of this probably lies in the fact that the patient lost a considerable amount of blood during his episodes of bloody diarrhea. Despite the administration of five whole blood transfusions before operation, there was little appreciable improvement in the blood picture. However, after operation the blood picture rapidly returned to normal.

Bloody diarrhea is more commonly associated with malignancy than with diverticula, and should be thoroughly investigated before a definite diagnosis is established.

The previous operation (appendicectomy) is not a contributing etiologic factor because there were no adhesions found near the ileocecal junction. The part involved in the fistula formation was the midportion of the ileum.

SUMMARY

A case of combined resection of a portion of ileum and colon for an ileocolic fistula due to malignant disease has been presented. This case demonstrates the fact that this complication may occur before the malignant disease has produced widespread metastasis and, therefore, combined resection is feasible and may produce a cure.

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ACUTE INTESTINAL OBSTRUCTION DUE TO ORANGE PULP BEZOAR

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THIS CASE REPORT is being made because a careful search of the literature fails to reveal any other case of acute intestinal obstruction due to such a cause. This was a case of acute intestinal obstruction due to the rapid ingestion of five fresh Florida oranges. While ordinarily this might have caused no difficulty, the present case had a dumping-stomach following gastric resection and a Pólya-anastomosis. Apparently, orange pulp was retained in the stomach and formed a bezoar. When finally expelled into the jejunum it was small enough to pass, but on arriving at the ileum, which is smaller in diameter, it produced obstruction.

Phytobezoars, composed of vegetable fibers, comprise about 40 per cent of the reported cases of bezoars. They are made up of stems, skins, fibers, or seeds, in the meshes of which may be included other food and epithelial detritus. Pyloric obstruction seems to be a predisposing factor. Rapidity of ingestion is important, bezoars probably being formed at one time, since no layers of accretion are found.

Persimmon seeds lead the list of etiologic agents, making-up the offending fibers in 75 per cent of the cases. Other substances reported are skins and seeds of prunes, plums, dried peaches or raisins; celery; cocoanut fiber and tobacco.

To have intestinal obstruction due to a phytobezoar is rare. Recently, however, three case reports have come from England of intestinal obstruction due to phytobezoars composed of dried peach.

Case Report.—No. 66915: Mr. E. S. was admitted to the Hospital on 2-20-'46 at 7:20 P.M. The patient had awakened on the day of admission with colicky pains throughout the abdomen. The pains gradually increased as the day wore on, and had begun to localize in the right lower quadrant of the abdomen for approximately two hours prior to admission. A white blood count done at this time showed 9,200, with 75 per cent polys. By noon the patient had vomited only once. He had had two bowel movements during the day, one at 8:00 A.M., and one at 11:00 A.M. Nothing abnormal was noted about the movements, excepting that the cramps were aggravated following the bowel movement and there was an almost constant desire to go to stool. By 7 o'clock that evening, the patient was in considerable pain. The pain had localized quite well in the right lower quadrant of the abdomen. Temperature 99°F., pulse 90. There was two-plus rigidity of the lower abdomen, chiefly on the right side. There was tenderness over McBurney's point as well as rebound tenderness. Rectal examination was essentially negative. The patient had the scar of a previous gastric resection and a Pólya-anastomosis, which was done for a recurrent peptic ulcer in 1940. The remainder of the examination was

essentially negative. *Preoperative Diagnosis:* First, acute appendicitis; secondary possibility, perforating peptic ulcer.

Operation.—Dr. Robert Bruce Malcolm: Incision was made over the lower right rectus. The muscle was displaced laterally and upon opening the peritoneal cavity, there was encountered a considerable amount of slightly blood-tinged fluid. This fluid did not suggest the appearance of a perforation. The appendix was then located, exposed, and found to be normal, aside from its extreme length. Exploration of the upper abdomen showed that the gastro-enterostomy was apparently functioning well. There was no evidence of a perforation. On exploring the pelvis, a loop of ileum was brought up which was found to be markedly enlarged, greyish in appearance and about twice the normal caliber. This looked like a fibroma, but an incision made longitudinally on the antimesenteric border disclosed a mass which, when extruded, was found to consist of orange pulp. After further exploration the bowel was sewed with two layers of sutures and replaced. The appendix was removed. The abdominal wall was closed in layers without drainage. The patient had an essentially uneventful postoperative course.

SUMMARY

A case of intestinal obstruction due to orange pulp is reported, which case is believed to be first of its kind in the literature.

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